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Introduction. Mismatching of patients and specimens can lead to incorrect histopathological diagnoses. Most misidentification errors in laboratories occur during the manual pre-laboratory and laboratory phases. In the past few years, we have examined this vital and challenging issue in our unit and introduced appropriate procedures. Recently, we have paid special attention to the problem of specimen mix-ups in the gross examination phase and the mismatching of blocks and slides in the cutting phase.

Objective. We have focused on the reduction of the potential sources of mismatching of specimen containers, tissue blocks and slides, focusing in particular on the most critical steps which are gross cutting and preparation of microtome sections.

Design. A 2D bar code directly printed on the labels of specimen containers and, directly printed onto cassettes and slides, is now being used; in addition, the system performs an electronic cross-check of tissue blocks and slides, which is managed by the laboratory information system.

Results. The present system permits full sample traceability from the moment samples reach the laboratory to the issuing of the final report. Indeed, the LIS records samples, blocks and slides in real time throughout the entire procedure, as well as the operator’s name, and the date and time each individual procedure is done. This facilitates later monitoring of the entire workflow.

Conclusions. The introduction of 2D bar code and electronic cross-checking represents a crucial step in significantly increasing the safe management of cases and improving the quality of the entire work process.

Cytologic re-evaluation of negative effusions from patients with malignant mesothelioma
V. Ascoli, D. Bosco, C. Carnovale Scalzo

Background. Cytology is a controversial means of diagnosing malignant mesothelioma due to the high rates of negative samples. The aim of the present study was to review effusions originally reported as “negative” in patients with histologically-proven mesothelioma to evaluate possible pitfalls.

Methods. We reviewed the cytologic slides of 25 specimens that refer to 15 epithelioid, 5 biphasic, 4 sarcomatoid and 1 well-differentiated papillary mesotheliomas. For comparison, we also reviewed 23 specimens from non-neoplastic conditions. For each effusion, we evaluated the background and calculated a score considering the following items: amount of mesothelial cells, architectural pattern and atypical features, and a revised diagnosis was rendered.

Results. More than half of the effusions initially called “negative” (but mesothelioma by histology) were considered atypical/suspicious (false-negative diagnosis); the remaining cases were true-negative or inadequate. Almost all effusions initially called “negative” (but non-neoplastic by histology) were considered negative. The only item that seems to discriminate between the two groups is atypia of mesothelial cells.

Conclusions. The present study has highlighted the following pitfalls: (i) to report effusions devoid of mesothelial cells as negative that instead should be reported as inadequate/non-diagnostic; (ii) to underestimate low cellular effusions containing atypical mesothelial cells or high cellular effusions containing bland mesothelial cells with a morular pattern; (iii) to consider that an inflammatory background may obscure a scant number of mesothelial cells. A categorized system (inadequate (M1), negative (M2), atypical (M3) and suspicious (M4)) for reporting effusion cytology may be of help in the diagnostic work-up of patients with effusions suspicious for mesothelioma.

Intra-operative frozen section technique for breast cancer: end of an era

Data on 2436 primary breast carcinomas diagnosed between 1992 and 2006 were collected to evaluate the rate of frozen section procedures performed over time. Frozen section procedures performed to evaluate resection margins for conservative surgery or sentinel node status were excluded. Over time, there was a decrease in the use of frozen sections indistinctly extended to all pT cancer categories. The rate of cancers diagnosed with frozen sections was 51.2% in 1999, and 0% in 2005-2006. In the same period, the adoption of cytology and core biopsy for breast cancer diagnosis increased from 40% in 1992 to more than 90% since 1999. In an audited diagnostic activity on breast pathology, the routine use of frozen sections on primary lesions was considered inappropriate, particularly in assessment of clinically non-palpable lesions, and should be limited to cases with inadequate pre-surgical sampling.

The diagnostic accuracy of cervical biopsies in determining cervical lesions: an audit
J. Wang, M. El-Bahrawy

Objective. The present audit was carried out to assess the diagnostic accuracy of cervical punch biopsy during colposcopy in comparison with diagnosis from subsequent cone excision.

Design and setting. Retrospective analysis was performed by examining the histopathology reports for paired cervical punch biopsies and cervical cone excisions for cases reported from April 2004 to March 2005 (when cervical biopsies and cones were reported by general pathologists) and from January to December 2008 (when reporting by specialist gynaecological pathologists was instituted).

Sample. 150 women had both cervical punch and cone biopsies performed in the 2004-2005 period, while 149 women had both biopsies performed in 2008.

Main outcome measures and results. In 2004-5, the rate of consistent diagnosis was 68.7%, compared with 75.8% in 2008. This was due to a decrease in the rates of overdiagnosis (16.7% vs. 14.8%) and underdiagnosis (14.7% vs. 9.4%), which was statistically significant. The sensitivity rates for 2004-5 and 2008 were 87.5% and 89.7%, and the specificity rates for the same periods were 39.8% and 39.4% respectively.

Conclusions. This audit highlights the importance of planning patient management on the basis of co-ordinated information from smear results, history, colposcopy findings and cervical biopsies. The introduction of specialist gynaecological histopathology reporting has significantly improved the rates of consistent diagnosis.

“Combined” desmoplastic melanoma of the vulva with poor clinical outcome
G. Collina

Desmoplastic melanomas in an unusual variant of melanoma that usually occurs in sun-damaged skin of elderly people. Desmoplasia may be the prominent features of the lesion or represent a portion of an otherwise non-desmoplastic melanoma; these latter are called “combined” desmoplastic melanoma. Desmoplastic melanomas of the vulva are rare. Herein, we report a case of “combined” DM of the labia minor consisting of a superficial spitzoid component and a deeper spindle desmoplastic component. Protein S-100 expression was ubiquitous, while MART-1 and HMB-45 were limited to the superficial spitzoid component and were nega-
tive in desmoplastic areas. Notably, the nodal metastasis retained the same biphasic pattern seen in the primary tumour. The patient died of widespread metastatic disease 3 years after diagnosis.

Case reports

Tuberculosis of superficial lymph nodes, a not so rare event to consider in diagnosis. A case in an elderly male
A. Merante, M.R. Ambrosio, B.J. Rocca, A.M. Condito, A. Ambrosio, M. Arvaniti, G. Ruotolo

Tuberculosis (TB) is still one of the most frequent infectious diseases worldwide. Until the 1990s, Western European countries showed a low frequency of TB infection, but the rise of immigration has led to a rapid increase in its occurrence. In the elderly, TB is emerging as a significant health problem (age-related decline of the cell-mediated immunity, associated illnesses, use of immunosuppressive drugs, malnutrition, poor life conditions), although its detection and diagnosis is not easy also considering its subclinical presentation. Almost 70% of all TB infections in Italy are found in the lungs; 50% of the extrapulmonary infections affect lymph nodes. Due to the low incidence of superficial tuberculous lymphadenitis without pulmonary manifestations, the possibility of a TB aetiology is often not taken into consideration in the differential diagnosis of lymphadenopathy, resulting in significant delay of appropriate treatment.

Herein, we describe the case of a 78-year-old male with nocturnal fever, weakness, night sweats, loss of weight and decay in general condition. The patient had a past medical history of prostate adenocarcinoma treated with hormone therapy. The past medical history in association with clinical findings and laboratory data (anaemia, high titters of fibrinogen and reactive c-protein) led to the suspect of metastatic adenocarcinoma. Only histological and molecular biology findings allowed us to make a correct diagnosis of TB.

Adenolipoma of the skin
S. Karoui, T. Badri, R. Benmously, E. Ben Brahim, A. Chadli-Debbiche, I. Mokhtar, S. Fenniche

Adenolipoma of the skin (ALS) is an uncommon histological variant of lipoma, characterized by the presence of normal eccrine sweat glands inside the fat proliferation. A 32-year-old woman presented to our department with a slow-growing, painless subcutaneous soft tumour located on the upper part of the right thigh. Microscopically, there was lobulated adipose tissue proliferation with well-differentiated eccrine glands and ducts in the periphery and centre of the nodule. These features were suggestive of ALS.

ALS is a rare microscopic variant of cutaneous lipoma having similar clinical features to lipoma. The most frequent locations of this tumour are thighs (as in our patient), shoulders, chest and arms. Histologically, the tumour is composed of lobulated adipose tissue with larger and more prominent lobules than those in normal subcutaneous adipose tissue. A well-developed capsule may also be identified. Eccrine glands and ducts, without proliferative changes, are well-differentiated within the adipose tissue. Differential diagnosis of adenolipoma includes the common lipoma and its variants, skin tag and other hamartomatous lesions, such as nevus lipomatosus superficialis, and the lipomatous variant of eccrine angiomatous hamartoma.

Adenomatous transformation in a giant solitary Peutz-Jeghers-type hamartomatous polyp
F. Limaiem, S. Bouraoui, A. Lahmar, S. Jedidi, S. Aloui, S. Korbi, S. Mzabi

Solitary Peutz-Jeghers-type polyp is a rare hamartomatous polyp without associated mucocutaneous pigmentation or a family history of Peutz-Jeghers Syndrome. It is usually encountered in the small intestine, but rarely involves the rectum. A 27-year-old previously healthy female patient presented with a two-month history of rectal bleeding. The patient had neither mucocutaneous pigmentation nor a family history of gastro-intestinal polyposis. Endoscopic examination revealed a solitary lobular polyoid lesion in the lower rectum. The polyp was sessile and measured 15 cm in diameter. As histological examination of the biopsy specimen was suggestive of adenoma, endoscopic polypectomy was performed. Histologically, this polyp had an arborizing muscular network originating from the muscularis mucosa, and was covered by well organized mucosa with several foci of dysplastic glands. The final pathological diagnosis was solitary Peutz-Jeghers type hamartomatous polyp with adenomatous transformation.
The role of 2D bar code and electronic cross-matching in the reduction of misidentification errors in a pathology laboratory. A safety system assisted by the use of information technology

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Key words
Mismatch errors • Risk management • 2D Barcode technology • Safety management of patient specimens

Introduction

Mismatching of patients and specimens can lead to incorrect histopathological diagnoses. Most misidentification errors in laboratories occur during the manual pre-laboratory and laboratory phases. In the past few years, we have examined this vital and challenging issue in our unit and introduced appropriate procedures. Recently, we have paid special attention to the problem of specimen mix-ups in the gross examination phase and the mismatching of blocks and slides in the cutting phase.

Objective

We have focused on the reduction of the potential sources of mismatching of specimen containers, tissue blocks and slides, focusing in particular on the most critical steps which are gross cutting and preparation of microtome sections.

Design

A 2D bar code directly printed on the labels of specimen containers, and directly printed onto cassettes and slides, is now being used; in addition, the system performs an electronic cross-check of tissue blocks and slides, which is managed by the laboratory information system.

Results

The present system permits full sample traceability from the moment samples reach the laboratory to the issuing of the final report. Indeed, the LIS records samples, blocks and slides in real time throughout the entire procedure, as well as the operator’s name, and the date and time each individual procedure is done. This facilitates later monitoring of the entire workflow.

Conclusions

The introduction of 2D bar code and electronic cross-checking represents a crucial step in significantly increasing the safe management of cases and improving the quality of the entire work process.

Introduction

Since the publication of “To err is human” in 1999, substantial work has been done to reduce factors that contribute to errors in medical and surgical pathology practice. Procedures in the histopathology unit involve multistep processes with several handoffs of materials, which are all potential sources of error. Errors that may occur at any stage of processing vary in frequency, depending on the laboratory. Several papers have been published that analyze and propose solutions. Over the past five years, we have approached this challenging issue in our laboratory, with particular focus on the pre-laboratory and laboratory phases. The most critical step is the accession phase, which is characterized by incorrect patient identifications and incorrectly-recorded laterality and anatomical sites. Another two steps in the procedure that are particularly prone to error are the gross and cutting phases, which are characterized by sample mix-ups and block and slide mismatching errors.

A significant reduction in the number of misidentification errors on accession was achieved in 2008 with the elimination of handwritten requests and handwritten labels, and by the introduction of an order entry with electronic requests and labels. In addition, direct printing of cassettes and slides by automatics printers interfaced with the laboratory information system produced a considerable reduction in block and slide mismatching errors.

However, data analysis in 2009 revealed continuing block and slide mismatching. For this reason, at the be-
Accuracy of a 2D bar code was introduced, which is directly printed onto container labels, cassettes and slides, in order to reduce mismatching in the gross examination and cutting phases. This new technology is also an effective means of improving sample traceability during the workflow.

The purpose of the present work is to discuss the highly reliable work procedure we have developed, which fully utilizes the benefits of information technology.

Materials and methods

The entire process was reorganised in May 2008 when a new laboratory information system (LIS, Armonia Dedalus, SpA, Italy) was integrated with the Hospital Information System (HIS; Trak-care, Traksytem, Australia), with an HL7 interface for receiving orders from physicians through HIS order entry. This eliminated the need for handwritten requests and handwritten container labels. At the same time, the LIS was interfaced with the cassette and slide printers (Leica Microsystems, Bannockburn, IL) to handle cassette and slide printing case-by-case during the gross and cutting phases; this avoids the need for manual code transcription. All of the above has been described in detail in a previous publication. Since 2010, the LIS has used a 2D bar code and has been interfaced with both cassette and slides printers (a Leica printer in the Cytology Lab and Slide Mate printers [Thermo Fisher Scientific, Waltham, MA] at the Cutting Station); the LIS also has been integrated with a Leica BOND-III instrument, which fully automates immunohistochemistry work; 2D bar codes are directly printed onto immunohistochemistry slides at the cutting station: the BOND-III reads the 2D slide bar codes. Extensive bar code printing testing and validation for cassettes and slides was conducted by Leica, Thermo Fisher Scientific and Dedalus, and for scanner configuration by the Dedalus Company and Metrologic Instruments Inc. We chose the Metrologic MS1690 Focus, which is an omnidirectional scanner capable of reading all standard 1D and 2D bar codes.

During set up, we carried out ping testing on cassettes and slides. No input failure occurred. Bar code misreading may be caused by poor quality cassette and slide materials, which can cause variations in printing quality. We always test any new material that will be used. The following are printed on cassettes: the accession code (e.g. 11-I-13500), specimen container letter (e.g. A, B, C), subpart block number (e.g. 1, 2) and a 2D bar code, which includes a progressive printing number (Fig. 1).

The following is printed on the slides as human readable text: accession code (e.g. 11-I-13800), patient name and surname, type of stain (e.g. HE, PAS), the name of our unit (Anat Pat, RN); in addition there is a 2D bar code, which also encodes a progressive printing number. The progressive printing number, found in both slide and cassette 2D bar codes, is essential for the univocal matching of a block and its associated slides. It is impossible for two identically identified blocks or slides to exist. For example, if a slide is printed and then the same slide is printed again, the first slide printed is identified in the 2D bar code as 11-I-13500A2 and the second one 11-I-13500A22.

This is of fundamental importance and is a key point regarding matching of blocks and slides.

Each workstation in our unit is equipped with a PC, monitor and scanner. We have also equipped each cutting station with small slide printers to avoid the need to preprint slides. The LIS manages each individual step via the 2D bar code regarding the processing of samples, blocks and slides by recording the name of the operator and the date and time of the step; in this way, each single case is traceable during the entire workflow.

The LIS furthermore records any error or problem detected at any stage in the workflow. This function is quick and easy to access by using a keyboard; in this function, a list of predetermined parameters are displayed: e.g. error or problem type, possible corrective action, date, time and operator. Cases where an error has been detected are marked by a special icon, so that the pathologist is alerted and can check the validity of the corrective actions taken before diagnosis.

Errors and problems are subdivided in the following way: accession errors, specimen errors or problems, and misidentification during the processing procedure. Each subgroup is further divided into other sub-categories (e.g. misidentification during gross examination, embedding, cutting, etc.). This system permits rapid analysis of collected data. Once a month, a specially trained technical staff member evaluates data trends.

The unit’s workflow, which is bar code based, is described in a consistent and easy-to-read manner.

1. **Accession phase:** after a double check to verify that data on the electronic request corresponds to that on the medical report that accompanies specimens (e.g.
bronchoscopy, endoscopic report, etc.), the case is entered into the LIS by scanning a bar code on the paper copy of the electronic request, determining the recovery of the request from HIS (Fig. 2). The LIS provides a lab worksheet with number (e.g. 11-I-14500) both as readable text and as a bar code (Fig. 3), and also provides labels for specimen containers in readable text as well as a 2D bar code. Once a misidentification error is detected, the case is rejected and it will be processed after the error has been corrected.

2. **Gross examination phase**: the specimen containers are moved to the gross bench for sectioning and recording of macroscopic findings. Our LIS provides many predetermined parameters for each anatomical site and each medical procedure; for example, the topographic code (SNOMED), the number and colour of the cassette (orange for urgent cases, white for sentinel lymph nodes, yellow for small biopsies, blue for lymph nodes, pink for skin biopsies and green for surgical specimens), section number, and the routine stains or immunostains, if provided. The default setting may be modified at any time during the process. Cassettes are directly printed (Leica Microsystems, Bannockburn, IL) case-by-case during gross examination. The printing process is quick and easy.

3. **Tissue embedding phase**: after processing each cassette is read by the scanner before embedding the tissue. The LIS displays the following: code number, tissue type, fragment number and notes, if recorded during gross examination, including operator name, date, time and status (Fig. 4); after reading, the cassette’s status is changed from *processing* to *executed*. When all samples related to a single case are embed-
4. **Cutting phase:** just before cutting, the operator reads the block’s bar code with the scanner, and the slide printer prints all the associated slides; after section cutting (and only at this time - before it is picked up) the slide is read by the scanner. If the slide does not match the block, a message error on the monitor alerts the operator (Fig. 5). The LIS displays the changing status of the slide from requested to validated only if the slide matches correctly. When all slides related to a single case are validated, the case’s status is changed from embedded to cut.

5. **Checkout phase:** at the end of the entire work flow procedure, there is the final check before delivering slides to the referring pathologist. Each slide is read by the scanner, and when all slides of a single case (routine staining, special stains and immunostains) are ‘pinged’ the case is ready to be sent for medical examination.

### Results

The results achieved have been particularly good and of significant importance. Since the introduction in 2010 of 2D bar codes on container labels, we have not had a single case of sample mix up in the gross examination phase in a total of 26,964 histological cases. In the gross examination phase, each case begins with a reading of the 2D bar code on the container label, and the LIS makes it impossible for a code number that is different to the case number in question to be printed on a cassette. In contrast, in 2009 we had 10 errors in a total of 26,961 (0.03%) cases that involved mismatch of samples from the same patient.

Additionally, in the cutting phase we have had no mismatch since automatic cassette and slide cross checking was made possible by the introduction of 2D bar codes in 2010 (26,964 histological cases; 80,571 tissue blocks). In contrast in the same period in 2009, we had 32 mismatches from a total of 26,961 cases (0.11%) (80,361 tissue blocks) caused by the transfer of sections from one block to a mismatched slide. Data analysis showed that mismatch errors were more or less equally distributed between routine cutting (14 cases) and re-cutting. There was a slightly greater error prevalence for re-cutting (18 cases), where the errors involved cases with similar code numbers (e.g. 09-I-23715 and 09-I-23915); 12 of 18 errors involved specimens from different patients, and 4 of 18 involved different specimens from the same patient. Of the 14 routine cutting mismatch errors, 10 involved different patients. None of the errors for either the gross examination or the cutting phase resulted in adverse consequences for the patient, as they were detected during subsequent steps. The errors were noticed in some cases because the clinical information was not concordant with histological appearance. In other cases, the slide samples clearly did not correspond with the anatomical site indicated in the request when viewed under the microscope. Another particularly important result achieved by the introduction of 2D bar coding is the introduction of automated tracing; it is now possible in real time, to trace a specimen container or missing block and locate it immediately.

Indeed, the LIS manages the workflow, step by step, recording the operator’s name, date and time of each single step. We are now able to know what is happening in real time, and to take immediate action to locate a misplaced container or block.

### Discussion

The case-by-case direct printing of bar code numbers on cassettes and slides by automated printers managed by the LIS prevents errors caused by handwritten labels and by transcription. Checking correspondence between the code number on container labels and the cassette at the gross station and between block and the slide at the cutting station was previously done visually and was therefore subject to error caused by fatigue and lack of concentration. Even if the mismatch rate was low in the gross examination and cutting phases, and in keeping with data reported in recent literature, an error that mismatches a slide to the wrong patient can have serious consequences on clinical outcome.

For this reason, we worked closely with the LIS provider to design a system that would prevent this type of error. The result is that we have up-graded our LIS with the introduction of 2D bar codes on labels of specimen containers, and direct printed on cassettes and slides. The biggest leap in improved quality was achieved by the introduction of electronic cross-match managed by LIS. Another important advance is that there is now sample traceability throughout the entire workflow.

In a recent paper, Zarbo et al. describes a workflow dependent on bar code reading and illustrates the use of traditional bar codes on specimen container labels, in specific labels for slides and use 2D bar code only for cassettes.

Unfortunately, in their laboratory, electronic requests are not yet employed and cases are accessioned manually from handwritten requisitions, which are often incomplete and unclear, as noted by Dimenstein. The labelling of slides represents an additional manual step that is time consuming, prone to error and finally more expensive than directly printing on them.

The electronic checking introduced in the cutting station overcomes the problem of operators failing to follow standard procedures, which was an issue that Zarbo emphasized in his report. The LIS prevents proceeding to the next case and alerts the operator if procedures are not followed. Furthermore, if the slide’s bar code is not
read by the scanner, the case is not validated. The intro-
duction of electronic cross checking of blocks and slides
is an effective means of preventing inevitable human er-
ors in the cutting phase caused by fatigue, lack of con-
centration and heavy workload.

During the development of this project, the only con-
cern was the possible increase in processing times. How-
ever, during the first three weeks after the adoption of
the new workflow we experienced only a small delay in
slide delivery, which was caused by the need to train
all operators; such training is obviously necessary when
introducing new organizational procedures. All techni-
cal staff have very positively accepted this new working
procedure. In addition, in recent years much has been
accomplished in training all operators in risk manage-
ment, and on-going work has been done with the entire
team to identify the causes of mismatching and improv-
ing workflow. The knowledge of when, where and why
misidentification errors occur, which is a fundamental
prerequisite for their successful reduction, has been fa-
cilitated by the LIS, which allows quick, easy and com-
plete error reporting at each step of the work flow, as
previously described.

In summary, the work over the last few years has been
focused on simplifying workflow procedures as much as
possible by utilizing information technology, and the em-
ployment of bar coding to minimize operator caused error.
The process was streamlined by eliminating some poten-
tially error prone procedures, most importantly eliminat-
ing manual accession input in the LIS by using a direct
electronic request entry. It is important to note that in this
manner, the patient and his or her samples are correctly
identified at the time they are taken, in the place they are
taken and by the clinician who performed the medical
procedure, and not later in the pathology lab by a member
of administration or technical staff. During gross tissue
examination, LIS case data can be accessed by reading
the 2D bar code on container labels, avoiding mix-up of
specimens; the direct printing of cassettes one case at a
time avoids the need for them to be prepared in advance
and eliminates the risk of confusing cassettes from dif-
ferent patients. The direct printing of slides, one block at
a time, at the moment of cutting of sections, eliminates
the need for labelling, which is a time consuming step.
More importantly, it also eliminates a potential source of
error because traditional labelling is a manual procedure
that is visually checked. Furthermore, labelling is more
expensive than direct printing of slides. The introduction
of electronic cross-checking using 2D bar codes directly
printed onto blocks and slides represents a very important
qualitative leap. In our experience, it represents the best
method for avoiding block and slide mismatching.

The redesigned workflow with 2D bar codes has an-
other advantage: real time case traceability throughout
the entire procedure. Gradually we redesigned the entire
workflow procedure over a period of years. The support
we received from top management was crucial for its
success. In our experience, no single piece of technology
can eliminate errors in a complex system such as a pa-
thology work flow composed of multiple handoffs. Each
laboratory has to consider the individual requirements of
their own workflow.

The LIS and bar code technology play a leading role in
making the entire process far safer. However, there is
also the need for standard operating procedures for each
step, accompanied by an efficient system of recording
effects for every phase (pre-lab, lab and post-lab) and rig-
orous daily compliance with all procedures.

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Cytologic re-evaluation of negative effusions from patients with malignant mesothelioma

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Key words
Mesothelioma • Cytology • Serous effusion • Reactive mesothelium • Diagnostic pitfalls

Summary

Introduction

Since most malignant mesothelioma (MM) first present with a pleural/peritoneal effusion, cytologic analysis represents the primary diagnostic approach. However, cytologic diagnosis of MM is notoriously challenging with a sensitivity ranging from 30% to 80%. This variability mainly reflects the lack of experience of pathologists with this rare malignancy and the complexity in interpretation of the changes in mesothelial cells, the main pitfall being the resemblance of mesothelioma cells to normal or reactive mesothelial cells. The lack of a dedicated technical approach to the handling of effusions is also the source of errors such as improper collection and processing of effusions fluids.

The topic of whether cytology should be an acceptable means of diagnosing MM is controversial, but a role for cytology cannot be excluded, also because cytology may be the only source of pathological material available.

Therefore, any information that could lend support to the possibility to suspect a diagnosis of MM in a fluid sample should be considered.

We present herein the experience of our laboratory on 25 cases of histologically-proven MM in which cytologic diagnosis on effusions was originally reported as negative for malignancy. Based on the re-examination of cytology specimens, we investigated the type of errors, if any, and produced a scoring system that might be helpful in detecting mesothelioma cells. For comparison, 23 negative effusions from histologically-demonstrated non-neoplastic conditions were also re-examined.

Materials and methods

From a series of 109 histologically proven cases of MM (all with a previous effusion examined) that were diag-
nosed in our institution (Azienda Ospedaliera Policlinico “Umberto I”, Roma) over a 9-year period, we retrieved 25 cases in which the original cytology report was “negative for malignancy”. Fourteen cases were first effusions and 11 were recurrent effusions. The final histologic diagnosis was as follows: epithelioid MM (n = 15), well-differentiated papillary mesothelioma (n = 1), biphasic MM (n = 5) and sarcomatoid MM (n = 4). Twenty-one were MM of the pleura and 4 of the peritoneum.

Cytological material consisted of conventional smears stained with Papanicolaou and Giemsa stains. None of the 25 specimens had been processed by the cell block technique. Also, immunocytochemistry had not been requested. The cytological slides were reviewed by the three coauthors who were non-blinded to the original diagnosis, and the following cytological features were considered: 1) background, defined in terms of inflammatory cells (lymphocytes, neutrophils, mixed inflammatory cells) and the presence of necrosis; 2) mesothelial cellularity, defined as absent, scarce, moderate, and abundant; 3) mesothelial cell architecture, the arrangement of mesothelial cells in clusters/morulae or as individual cells; 4) mesothelial atypical features, including anisonucleosis, atypical mitosis, multinucleation/macronucleoli, cytomegalia, vacuolation of the cytoplasm and presence of squamoid cells.

We calculated a score for each effusion considering the amount of mesothelial cells, architecture of mesothelial cells and number of atypical features (Tab. I). Based on morphological features and taking into account the total score, we formulated a revision diagnosis. To verify the performance of the scoring system, we also reviewed 23 effusion specimens from histologically-demonstrated non-neoplastic pleural conditions.

Results

Cytological revision

**Group negative by cytology/mesothelioma by histology**

The main features of cytological revision of the 25 MM cases together with the corresponding histological subtypes are reported in Table II, and in Figures 1-4.

- **Background.** All effusion samples were characterized by a variable amount of inflammatory cells.

There were two main patterns: neutrophil plentiful (Fig. 1), and small lymphocyte plentiful (Fig. 2). In effusions with abundant neutrophils, there was also a large amount of fibrin and necrosis obscuring mesothelial cells, when present (Fig. 3).

- **Mesothelial cells.** In 6 specimens, mesothelial cells were absent (inadequate/non-diagnostic specimens); in the other 19 specimens, mesothelial cells were present (adequate specimens). Of these 19 adequate specimens, 12 effusions were scarcely cellular and 7 moderate-to-abundant cellular.

- **Mesothelial architecture.** Mesothelial cells were seen either as scattered single cells (n = 11, Figs. 1-4) or as an admixture of single and clustered cells (n = 8, Fig. 5).

- **Mesothelial atypical features.** Of the 19 adequate specimens, 5 effusions showed mesothelial with no atypical features. The other 14 effusions showed

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**Tab. I. Scoring system.**

<table>
<thead>
<tr>
<th>Cytological features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mesothelial cellularity</td>
<td>From 0 to 3 points (0 = absent, 1 = scarce, 2 = moderate, 3 = abundant)</td>
</tr>
<tr>
<td>2. Architecture of mesothelial cells</td>
<td>From 1 to 2 points (1 = single, 2 = single &amp; clusters)</td>
</tr>
<tr>
<td>3. Atypical features of mesothelial cells (anisonucleosis, multinucleation, atypical mitosis, macronucleoli, cytomegalia, vacuolation of the cytoplasm, presence of squamoid cells)</td>
<td>From 1 to 7 points</td>
</tr>
</tbody>
</table>

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*Fig. 1. Single mesothelial cells surrounded by neutrophils; note cytomegalia, multinucleation and prominent nucleoli. Histology revealed epithelial mesothelioma. Cytodiagnosis on revision: M4/ suspicious.*
often multinucleation and macronucleoli and cytomegaly (Figs. 1, 3), also in addition to vacuolation of the cytoplasm and squamoid cells (Fig. 4); the least frequent atypical features were anisonucleosis and mitosis.

Upon revision, we attributed the 25 effusions to 4 categories: M1 (inadequate), M2 (negative), M3 (atypical) and M4 (suspicous).

**M1-Inadequate/non-diagnostic.** We included 6 cases in this category that were completely devoid of mesothelial cells. The background of the smears was heavily inflammatory (granulocytes or lymphocytes). The overall score was 0.

**M2-Negative.** We included 5 cases with a low number of mesothelial cells lying singly (n = 4) or in clusters (n = 1), and with no atypical nuclear features. The background of the smears was heavily inflammatory; often there were granulocytes and also abundant necrosis. The overall score was 2.

**M3-Atypical mesothelial cells of undetermined significance.** We included 8 effusions in this category characterized by scarce rather than moderate mesothelial cellularity; mesothelial cells were seen as single cells (n = 6) more than in clusters (n = 2); mesothelial cells showed a few atypical nuclear features; the inflammatory background was mainly represented by lymphocytes (Fig. 2). A single case included in this category was highly cellular, but anisonucleosis was the only atypical feature of mesothelial cells. The overall score was between 3 and 5.

<table>
<thead>
<tr>
<th><strong>Histologic subtype</strong></th>
<th><strong>Background</strong></th>
<th><strong>Cytological revision</strong></th>
<th><strong>Diagnosis on revision</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inflammatory</td>
<td>Mesothelial cells</td>
<td>Diagnosis on revision</td>
</tr>
<tr>
<td></td>
<td>Cell Type</td>
<td>Amount Architecture</td>
<td>Atypical features</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Lymphocytes</td>
<td>0 NA NA NA 0</td>
<td>Inadequate/non-diagnostic (M1)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Neutrophils</td>
<td>0 NA NA NA 0</td>
<td>Inadequate/non-diagnostic (M1)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Neutrophils</td>
<td>0 NA NA NA 0</td>
<td>Inadequate/non-diagnostic (M1)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Neutrophils</td>
<td>0 NA NA NA 0</td>
<td>Inadequate/non-diagnostic (M1)</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>Lymphocytes</td>
<td>0 NA NA NA 0</td>
<td>Inadequate/non-diagnostic (M1)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Mixed</td>
<td>0 NA NA NA 0</td>
<td>Inadequate/non-diagnostic (M1)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Neutrophils/Necrosis</td>
<td>1 1 0 2</td>
<td>Negative (M2)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Mixed</td>
<td>1 1 0 2</td>
<td>Negative (M2)</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>Neutrophils/Necrosis</td>
<td>1 1 0 2</td>
<td>Negative (M2)</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>Mixed</td>
<td>1 1 0 2</td>
<td>Negative (M2)</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>Lymphocytes</td>
<td>1 1 0 2</td>
<td>Negative (M2)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>1 1 1 3</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Lymphocytes</td>
<td>1 1 1 3</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Lymphocytes</td>
<td>1 1 2 4</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>1 1 2 4</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>2 2 1 5</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>2 1 2 5</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>1 2 2 5</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>1 1 3 5</td>
<td>Atypical (M3)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Mixed</td>
<td>2 2 2 6</td>
<td>Suspicious (M4)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Lymphocytes</td>
<td>1 2 3 6</td>
<td>Suspicious (M4)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Mixed</td>
<td>2 2 2 6</td>
<td>Suspicious (M4)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Mixed/Necrosis</td>
<td>2 2 2 6</td>
<td>Suspicious (M4)</td>
</tr>
<tr>
<td>WDPM</td>
<td>Mixed</td>
<td>3 2 2 7</td>
<td>Suspicious (M4)</td>
</tr>
<tr>
<td>Epithelial</td>
<td>Neutrophils</td>
<td>2 2 4 8</td>
<td>Suspicious (M4)</td>
</tr>
</tbody>
</table>

NA = not applicable
WDPM = well-differentiated papillary mesothelioma
M4-Suspicious mesothelial cells. We included 6 effusions characterized by moderate/abundant mesothelial cellularity; in all specimens, there were clusters of mesothelial cells (Fig. 5); the number of nuclear atypical features was variable. The overall score was > 5.

Group negative by cytology/negative by histology

The main features of the cytological revision of the 23 non-neoplastic cases are reported in Table III.
- **Background.** All effusion samples were characterized by a variable amount of inflammatory cells.
- **Mesothelial cells.** In a single specimen, mesothelial cells were absent (inadequate/non-diagnostic specimen); most other specimens contained a moderate amount of mesothelial cells.
- **Mesothelial architecture.** Mesothelial cells were seen either as scattered single cells or as an admixture of single and clustered cells.
- **Mesothelial atypical features.** Of the 22 adequate specimens, effusions showed no atypical features.
Upon revision, we attributed the 23 effusions to 2 categories, M1 (inadequate) and M2 (negative).

**M1-Inadequate/non-diagnostic.** We included a single case in this category that was completely devoid of mesothelial cells. The background of the smears was heavily inflammatory (granulocytes).

**M2-Negative.** We included 22 cases with a moderate number of mesothelial cells lying singly or in clusters and with no atypical nuclear features or minimal atypical features. The background of the smears was inflammatory. The overall score was between 2 and 6.

**Discussion**

Our results showed that the cytologic revision of specimens previously reported as negative (but mesothelioma by histology) provided a different diagnosis in 56% of cases. These effusions represent diagnostic errors (false-negative diagnoses) because they contained atypical mesothelial cells. When excluding 6 inadequate specimens (24%), the remaining 5 cases (20%) were confirmed as negative for malignancy, and were not diagnostic errors (true-negative diagnoses) by cytology.

The scoring system is not particularly useful in separating the effusions due to non-neoplastic conditions from effusions due to mesothelioma. However, there is a bias of case selection in the MM group. In fact, effusions due to MM were cases that had been called “negative” in earlier diagnosis; it is likely that effusions containing clear-cut mesotheliomatous cells would give a higher score. Architectural features seem to be a non-informative variable, and the amount of mesothelial cells does not discriminate between the two groups; rather, it seems that more abundant mesothelial cells characterize the “negative” effusions more than “false negative effusions” due to mesothelioma. Atypical features are probably the most useful charac-
teristics in the daily practice to discriminate between the two groups.

Based on our diagnosis on revision, we propose that effusions containing atypical mesothelial cells should be called at the very least “effusions containing atypical mesothelial cells of undetermined significance” (M3 category); those effusions containing abundant mesothelial cells with a morular pattern with some atypical features should be called “suspicious for mesothelioma” (M4 category). The M3/atypical and M4/suspicious effusions are at variance more on the basis of the amount of mesothelial cells and on the basis of cell grouping, rather than on the number of atypical nuclear features. We also propose, similar to thyroid/breast and cervical cytology, a system for reporting effusion cytology that could be of help in the diagnostic work-up of fluids for mesothelioma: inadequate (M1), negative (M2), atypical (M3) and suspicious (M4), as recently reported 1.

Although we are aware of the limits of cytology in diagnosis of mesothelioma, and confirmed herein, the present study has allowed us to focus on the following pitfalls: (i) To call negative those effusions that are devoid of mesothelial cells; these effusions should be called inadequate/unsatisfactory, non-diagnostic. Any specimen with no mesothelial cells to be evaluated should be unsatisfactory for evaluation, as in thyroid and cervical cytology. (ii) To pay little attention to low cellular effusions containing atypical mesothelial cells dispersed as single cells. Several conditions limit exfoliation of diagnostic cells into effusions (recurrent effusions, non-epithelial mesothelioma). Any specimen with abnormal cells should be satisfactory for evaluation, as for cervical/thyroid cytology. In such cases, a note should be added indicating that the presence of mesothelioma cannot be excluded. (iii) To not take into account high cellular effusions with a striking morular pattern of mesothelial cells of bland appearance. Another pitfall is the heavy inflammatory background that may hamper the diagnosis by obscuring the scant number of mesothelial cells. In the atypical/M3 category, we noticed that inflammatory cells were mainly lymphocytes; interestingly, it is known that mesothelioma can be heavily infiltrated with many immune effector cells, with T-lymphocytes constituting the major part of inflammatory cells 7. Other factors (data not shown) that may have contributed to the diagnostic pitfall are: (i) the scarce amount of fluid examined respect to the amount of fluid evacuated implying hypocellular specimens; (ii) the improper specimen processing (excess of blood and insufficient concentration of cellular sediment); (iii) the absence of immunocytochemistry (because cell blocks are not routinely prepared in our laboratory in case of negative effusions).

Taking into account histology, effusions that also remained negative on revision included three of four sarcomatous MM of the present series; this finding is not unexpected and is a well-know feature in the cytologic literature (mesothelial cells are entrapped in the fibrous tissue). Among the suspicious/M4 effusions, there was a case of well-differentiated peritoneal mesothelioma (WDPM), which is an uncommon subtype of mesothelioma characterized by superficial spreading of papillary formations lined by bland epithelioid cells that can be a source of false-negative cytologic diagnoses. However, this entity should be recognized by cytology in highly cellular effusions and reliably be called suspicious for mesothelioma 8 9.

Conclusions

1. More than half of effusions due to mesothelioma that were initially called “negative for malignancy” are false-negatives on revision. The remaining cases are either true negatives (very scarce cellularity) or inadequate (absence of mesothelial cells).

2. Cytology may aid in diagnosis in patients with epithelioid and biphasic MM, but not in patients with sarcomatoid MM.

3. Obscuring inflammatory background (lymphocytes, neutrophils) and necrosis may hamper diagnostic evaluation of atypical mesothelial cells.

4. Currently, to limit the number of false-negative diagnosis, we ask clinicians to send the total amount of fluid that is actually collected to increase the amount of cells. We carefully process effusion fluid to routinely prepare cell-blocks, as strongly recommended by most experts.

5. As in thyroid/breast and cervical cytology, a categorized system for reporting effusion cytology may be of help in the diagnostic work-up of fluids for mesothelioma (inadequate [M1], negative [M2], atypical [M3] and suspicious [M4]).

6. The scoring system adopted in this study (evaluating the amount of mesothelial cells, architectural pattern and atypical features of mesothelial cells) is not particularly useful in separating effusions due to non-neoplastic conditions from those due to mesothelioma; nevertheless, atypical features are probably the most useful characteristics in the daily practice to discriminate between the two groups.
References


Intra-operative frozen section technique for breast cancer: end of an era

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Key words
Frozen sections • Intraoperative diagnosis • Breast cancer • Core needle biopsy • Fine needle aspiration cytology

Summary
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Introduction
The frozen section technique was first introduced by Wilson in 1905 for intraoperative diagnosis of breast carcinoma1. In subsequent years, intraoperative frozen section examination was established as a reliable procedure for the rapid histologic evaluation of surgical breast specimens2-6. Advances in radiology, pathology, surgical techniques, medical oncology and radiotherapy have changed the diagnostic and therapeutic approaches to breast cancer. Nowadays, different therapeutic strategies to breast cancer are available and tailored treatment for each individual patient is guided by detailed clinical and pathological data available before surgery. Over the years, the flow-chart referred to the assessment of breast lesions has been progressively shifted from intraoperative procedures to pre-surgical diagnostic techniques, as imaging guided fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) or vacuum-assisted gun needle biopsy (VAB)7-13. The diffusion of mammography has increased the detection of small cancers (< 1 cm) as well as proliferative, low grade atypical lesions for which intraoperative frozen sections (FS) should not be considered mandatory4-6,14-18. In this scenario, FS has lost its role as the first line diagnostic method guiding the surgical strategy on primary breast lesions19-21 through intraoperative assessment of a suspicious breast lesion, while an important role is still reserved to the evaluation of resection margins22-24 and status of sentinel lymph nodes25-27.

In the literature, only limited data have been collected with the aim of objectively defining the decreasing use of FS. The aim of the current study was to analyse the frequency of FS utilization in primary breast cancer series over a period of 15 years, and to evaluate the influence of clinical and pathological variables on results.

Materials and methods
Data on a large series of consecutive breast cancers, detected outside a screening program and surgically treated in “G.B. Rossi” University Hospital in Verona between January 1992 to December 2006 were extracted from files of the Breast Cancer Registry and the Department of Pathology of the same institution. The rate of breast cancers submitted to FS for intraoperative diagnostic purpose were retrieved from computerized diagnostic files of the Department of Pathology. Frozen section procedures performed to evaluate resection margins for conservative surgery or sentinel node status were excluded. According to the purpose of the present analysis,
cancers were stratified according to the year of detection, “in situ” or invasive cancer histology, lesion size measured on the histological slide and expressed in pT category according to the American Joint Committee on Cancer (AJCC)\(^{28}\). To match the number of cancers histologically diagnosed and the number of needle biopsies performed to gain a pre-surgical diagnosis, pathological files were also searched for pre-operative diagnostic procedures performed on primary breast lesions during the same period.

### Results

Between January, 1992 and December 2006, 2434 primary breast cancers were collected at the Department of Pathology of the University of Verona (Tab. I). Invasive breast cancers accounted for 85.6\% (2,084 cases) and “in situ” cancers for 13.5\% (329 cases). In 0.9\% of cases, the invasive or “in situ” type was not specified (21 cases). Over the years, the detection rate of invasive breast cancers smaller than 2 cm (pT1mic-a, pT1b, pT1c) showed a progressive increase balanced by the decreasing detection rate of cancers larger than 2 cm (pT2+) (Fig. 1). Changes in the distribution in the detection rate of breast cancer in favour of small lesions were observed during the middle of the 1990’s, but a higher detection rate was registered in 1999 and continued in subsequent years, favoured by the introduction of the breast cancer screening program and more participation of women in non-organized mammography tests. From 1992 to 1999, the rate of cancers submitted to FS was significantly influenced by cancer size with more FS performed on cancers larger than 1 cm (FS rate in pT1c cancers: 40\%; FS rate in cancers were submitted to FS, but in 2005 and 2006, no primary breast lesion was assessed with FS (Fig. 2). The progressively decreasing use of FS began in the middle of the 1990’s. At the beginning of the 2000’s, the requests for FS on primary breast lesions registered a nearly vertical decrease (Fig. 2). The decreasing use of FS on primary breast cancers involved all pT cancer categories (Fig. 3). From 1992 to 1999, the rate of cancers submitted to FS was significantly influenced by cancer size with more FS performed on cancers larger than 1 cm (FS rate in pT1c cancers: 40\%; FS rate in
pT2+ cancers: 48.7%). In the 2000’s, the FS rate was less than 2.5% in all pT cancer categories (Fig. 4).

Data on pre-surgical diagnostic procedures performed on surgically treated lesions were completely available for screen-detected breast cancers and have been previously published. All screen-detected breast cancers were assessed with FNAC or CNB before surgery. FNAC was adopted as a first-line method to obtain cytological smears from suspicious lesions with an accuracy that was well within the thresholds proposed by European guidelines for quality assurance in breast cancer screening programmes. Briefly, the FNAC positive predictive value for a malignant diagnosis was 99.3%, the inadequate rate from cancer (IRc) was 2.4% and the false-positive rate (FPR) was 0.5%.

Data on pre-surgical sampling diagnostic procedures performed on clinically detected cancers were available for about 60% of all cases for years between 1992 and 1997, but for subsequent years (1998-2006) more of 90% of cases were furnished with information about the needle sampling procedures performed. The rate of cancers submitted to a pre-surgical sampling procedure, either FNAC and CNB, increased exponentially since 1995 (Fig. 5), which was balanced by the decreasing use of FS (Fig. 2).

Discussion

The results of the current study about the use of FS on primary breast lesions during 15 years of surgical pathology activity (1992-2006), have shown the progressive disuse of this technique in our institution. A rate as high as 50% of primary breast cancers were submitted to FS in 1992, but at present no cancers are assessed with FS in an intraoperative setting (Tab. 1).

For many years, the diagnosis of breast cancer was guided by the intraoperative assessment of suspicious lesions by frozen sections. After long-lasting scientific discussions about accuracy of FS on breast lesions, pathologists...
achieved an overall agreement on the appropriate setting in which FS should be adopted. Trained personnel and accurate selection of lesions to be submitted to FS evaluation limited the false–negative rate to as less than 1%, and the number of deferred diagnoses to less than 5%. The appropriateness of FS examination for diagnosis of mammographically-detected lesions has been subject of controversy, and most authors have concluded that frozen section examination should be limited to cases with distinct gross lesions larger than 1.0 cm. As a consequence, the percentage of breast specimens evaluated by frozen sections has decreased over the years. A review of data from Ben Taub Hospital (Houston, USA) documented that, between 1985 and 1995, 20% to 35% of all intraoperative consultations sent to frozen section analysis were from the breast, but this decreased to 4-8% in the 2000’s. In our institution, the decreasing use of FS, already detectable in the middle of 1990’s, registered an acceleration at the beginning of 2000’s in concomitance with the beginning of screening programme activity (Fig. 2).

Screening programmes favour the detection of lower graded, smaller sized breast cancers as well as pre-invasive lesions and pure microcalcifications for which the feasibility of intraoperative consultation has been evaluated, but not routinely recommended. Studies suggest that FS for these breast lesions may have a lower accuracy and may impair the results of definitive histology from paraffin-embedded tissue due to freezing artefacts.

In the current cancer series, the beginning of the screening activity coincided with the growing detection of cancers smaller than 1 cm and the decreasing rate of cancers larger than 2 cm (Fig. 1). However, only 8% of breast cancers collected from 1999 to 2006 were screen-detected, and assume that the “positive” effect of screening programmes in stimulating women to perform mammography examinations favoured the improved detection of small breast cancers even in a female population that was not invited to screening represents 92% of the current series. The overall detection rate for cancers...
smaller than 1 cm shifted from 12-18% between 1992 and 1996 to 20-40% in subsequent years. The growing number of small breast lesions may be a cause of the reduced use of FS. The sensitivity of frozen section diagnoses of breast lesions after the introduction of a national programme in mammographic screening in Luxembourg dropped from 92.3% in 1990 to 87.6% in 1998, the negative predictive value from 95.7% to 88.3%, and invasive breast cancers ≤ 1 cm increased from 14.2% to 22.3% (p < 0.01). Breast frozen section examinations in 1990 compared to those in 1998 declined from 70.7% to 62.2%. Nevertheless, the decreasing use of FS is not completely explained by the increased detection rate of small cancers less than 1 cm. In current series, the decreasing rate of FS performed on primary breast cancers was observed in all pT cancer categories (Fig. 2). The comparison between the FS rate performed on breast cancers collected between 1992 and 1999 and the FS rate in cancer series between 2000 and 2006, stratified according to cancer size, highlights that in the 2000’s FS was exceptionally performed for diagnostic purpose on primary breast cancers, whatever the cancer size (Fig. 3). This is far more interesting for our analysis, especially if it is considered that in 2005 and 2006, on a total of 397 cancers, no FS was performed (Tab. I), even if 60% of detected cancers were larger than 1 cm and potentially amenable to FS (Fig. 1).

The strictly adherence to guideline recommendations favouring pre-surgical, image-guided needle assessment of breast suspicious lesions to avoid unnecessary surgery, aided the widespread adoption of FNAC, CNB and VAB to obtain a diagnosis on mammographically detected breast lesions. In a multidisciplinary approach to breast lesions, biopsy techniques provided optimal diagnostic accuracy with a sensitivity between 93% and 100% and a specificity between 98% and 100% which undoubtedly influenced the reduction of unresolved cases sent to FS. The type of breast lesion on mammograms or ultrasound (focal, parenchymal distortion, calcifications) and the confidence of the radiologist or pathologist with a needle sampling technique are guiding the modality to obtain diagnostic samples from breast lesions, reducing costs and limiting the use of FS to those cases in which a pre-surgical diagnosis is not adequate.

A preoperative core or fine-needle biopsy may eliminate unnecessary surgery and significantly reduce costs. The study of sentinel lymph node and schemes of neoadjuvant chemotherapy that increase breast conservation surgery, disease-free and overall survival in patients with complete pathological response, favoured the adoption of core needle biopsy for histological demonstration of breast carcinoma and for the assessment of a biological cancer profile predictive of response to medical therapy. In addition, preoperative diagnosis of invasive breast cancer increases the likelihood of clean margins at definitive surgery. This reduces the need for a two-stage procedure and improves both surgical and oncological outcomes.

Advances in surgical techniques, oncology, pathology, radiotherapy and radiology have influenced a new vision for treatment of breast cancer and reduced surgical trauma. The current results confirm that drastic changes have occurred in the management of breast lesions, with more patients evaluated in a pre-operative setting. After more than 100 years from its first adoption as a rapid method for breast cancer diagnosis, the use of frozen sections is no longer considered for primary breast lesions. In an audited diagnostic activity on breast pathology, the routine use of FS on primary lesions is inappropriate, particularly in the assessment of clinically non-palpable lesions. Its use should be limited to cases with inadequate pre-surgical sampling quantified in no more than 5% of surgically removed cancers.

References


Jensen JA. Breast cancer: should we investigate margins or redesign the surgical approach? J Am Coll Surg 2010;210:1012.


Introduction

In the UK, a cervical screening program has been implemented since the 1980s, and the advantages of cervical screening are well documented, with a decrease in both incidence and mortality from cervical cancers. Despite its success, cervical screening by cytology is not always reliable. It has been established that the average screening sensitivity and specificity of cervical cytology is about 61-66% and 82-91%, respectively. However, a positive cervical cytology result is only the first step in the pathway towards definitive diagnosis and treatment of a cervical lesion. The current practice in the UK is that a patient with a cytology result confirming definite dyskaryosis or with repeated borderline change requires referral to colposcopy. At colposcopy, the cervix is visualized and a punch biopsy is often taken for histological examination. If high grade cervical intraepithelial neoplasia (CIN) or cervical glandular intraepithelial neoplasia (CGIN) is confirmed on biopsy, the patient then undergoes cervical cone or loop excision.

Therefore, accurate diagnosis on the biopsy taken at colposcopy is key in directing further management of the patient. Despite the importance of this key step in the patient pathway, there have been few studies examining the reliability of cervical punch biopsies. One study analysed 352 cases and showed that there was a concordance rate of only 66% between the histological diagnoses of punch biopsies and the results of the subsequent loop excision of the cervix. In another study of 107 cases, cervical punch biopsy was compared to cytology. It was found that there was a consistency rate of 63% between cervical punch biopsies and cones. We investigated the accuracy of reporting of cervical biopsies taken at colposcopy, which would influence the subsequent management of patients. Moreover, the practice of histopathologists as a whole is moving towards specialist reporting. It also remains to be seen if such a move improves the accuracy of cervical punch biopsy
diagnosis. In this audit, we investigated the diagnostic accuracy of cervical biopsies performed at a gynaecological cancer centre. The accuracy of diagnosis in two different periods was analysed, a period during which the diagnosis of cervical biopsies and cones was done by general pathologists, and a period after specialist reporting by gynaecological histopathologists was instituted and the vast majority of cervical biopsies were reported by specialists.

Methods

Patients
This is a retrospective study of histopathology reporting on cervical punch biopsies and cones during two periods. The earlier period was from 1 April 2004 to 31 March 2005, and the later period was from 1 January 2008 to 31 December 2008. Only patients who had both a cervical biopsy and a subsequent cone biopsy reported at the Department of Histopathology, Hammersmith Hospital, during the periods defined were included.

Data collection
For each pair of specimens, pathology reports were retrieved and the following data collected: type of specimen, consultant histopathologist (general or specialist) reporting the case and diagnosis. In cases where the diagnosis fell between two categories, the higher grade diagnosis was recorded, as in most cases further management would be based on the higher grade disease. As examples, for the purpose of this audit in a punch biopsy reported as showing CIN 2-3, the diagnosis was considered as CIN 3 and for a punch biopsy where the diagnosis is CIN 1 and CGIN, the diagnosis was CGIN. Based on the diagnoses of the biopsies and cones, each pair of specimens was categorized as having consistent diagnoses, overdiagnoses or underdiagnoses. Situations of overdiagnosis and underdiagnosis are summarized in Table I.

For the audit purposes, since CIN2 and CIN3 are both high grade lesions which have similar management protocols, a biopsy of CIN2 with a subsequent cone excision showing CIN3, or vice versa, was classified as consistent diagnosis. This is in line with the Bethesda classification of high-grade squamous intra-epithelial lesions (HSIL). The same situation also applies for CIN2/3 and CGIN. However, CIN1 and human papilloma virus (HPV) infections were categorized separately, despite the similar management plans and the common Bethesda classification of low-grade SIL (LSIL). This is because these lesions have previously had different management strategies in the UK. In addition, a diagnosis of CIN (difficult to grade) or an inadequate sample at cervical biopsy was deemed to be consistent with any CIN grade in the cone excision. However, a biopsy diagnosis of CIN (difficult to grade) and a subsequent cone diagnosis of HPV only or benign conditions was considered overdiagnosis.

In addition to comparing the reporting accuracy between the two periods, the results were categorized into whether the reporting of the cervical punch biopsy was done by specialist gynaecological histopathologists, or by general histopathologists.

Standards
There have not been any previous publications that have dealt in detail with the problem of overdiagnosis or underdiagnosis in cervical biopsies. However, Boonkilit et al. have shown in their series that there is a concordance rate of 66% between cervical biopsy results and cones. For the purposes of the present audit, therefore, we have considered a consistent diagnosis rate of 60% to be acceptable. Also, Thompson et al. have shown that there was a negative diagnosis in cone excisions of 28-68%.

Thus, an overdiagnosis rate of less than 25% was considered acceptable.

Statistical analysis
To determine if the number of consistent diagnoses and the number of either over- or underdiagnoses were significantly different between the two periods of reporting, a chi-square test was performed. A significant difference in reporting accuracy was if the p value was < 0.05.

Finally, to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the two reporting periods, each diagnosis was categorized into positive results (high-grade lesions or higher, including CIN2, 3, CGIN and invasive cancer) or negative results (low-grade or benign lesions, including CIN1, HPV, atypia or inflammation). This classification was based on the management protocols for the diagnosis, with high-grade lesions being an indication for a cone excision. Biopsy samples which were CIN (difficult to grade) or inadequate were classified as consistent with the cone diagnosis (as described above).

Tab. I. Criteria for overdiagnosis and underdiagnosis.

<table>
<thead>
<tr>
<th>Overdiagnosis Criteria</th>
<th>Underdiagnosis Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2 or 3</td>
<td>CIN1/HPV/benign conditions</td>
</tr>
<tr>
<td>CIN1</td>
<td>HPV/benign conditions</td>
</tr>
<tr>
<td>CIN (difficult to grade)</td>
<td>HPV/benign conditions</td>
</tr>
<tr>
<td>Cervical punch biopsy</td>
<td>Cone biopsy</td>
</tr>
<tr>
<td>CIN1</td>
<td>CIN2 or 3</td>
</tr>
<tr>
<td>HPV</td>
<td>CIN 1, 2 or 3</td>
</tr>
<tr>
<td>CIN (any grade)</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Benign conditions/atypia</td>
<td>HPV/CIN/invasive carcinoma</td>
</tr>
</tbody>
</table>

Results

Cervical biopsy and cone results
From April 2004 to March 2005, a total of 744 cervical punch biopsies were reported. Of these, 150 cervical biopsies had subsequent cone biopsies done in the same period. The mean age of patients was 32 years (range
Diagnostic accuracy of cervical biopsies

In 2008 (January to December), the total number of cervical punch biopsies was 514, with 149 of patients having subsequent cone biopsies. The mean age of the patients for this period was 31 years (range 21-77).

In 2004-2005, the histological diagnoses of cervical biopsies were 13 CIN1, 64 CIN2, 42 CIN3, 2 CIN difficult to grade, 5 CGIN, 5 invasive carcinoma, 6 HPV and 13 benign lesion (e.g. cervicitis). Among the cone biopsies, there were 27 CIN1, 45 CIN2, 50 CIN3, 4 CGIN, 10 invasive carcinoma, 7 HPV and 7 benign lesion. The percentages of high-grade lesions diagnosed by cervical biopsies and at cone excision were 78.7% and 72.7%, respectively. Figure 1 shows examples of the different diagnoses in cervical punch and cone biopsies.

In 2008, among the cervical biopsies, there were 13 CIN1, 89 CIN2, 29 CIN3, 1 CIN difficult to grade, 2 CGIN, 3 invasive carcinoma, 2 HPV and 10 benign. Among the cone biopsies, there were 21 CIN1, 65 CIN2, 45 CIN3, 2 CGIN, 3 invasive, 2 HPV and 10 benign lesion. The percentages of high-grade lesions diagnosed by cervical biopsies and at cone excision were 83.2% and 77.2%, respectively.

Sensitivity and specificity of reporting

For the reporting period 2004-5, the sensitivity of the cervical biopsy was 87.5%, the specificity was 39.5%, the PPV was 81.0% and the NPV was 51.7%. In 2008, the respective values were 89.7%, 39.4%, 83.9% and 52%. The results are shown in Figure 2A.

Consistency of reporting

The results were categorized into cervical biopsies that were consistent with cone diagnosis, overdiagnoses or underdiagnoses. The results are shown in Tables II, III and IV respectively. There was an increase in the percentage of consistent diagnoses in 2008 (75.8%) compared with 2004 (68.7%), with decreases in both the incidences of over- (14.8% vs 16.7%) and underdiagnoses (9.4% vs 14.7%). The results are presented in Figure 2B.

Considering cases of overdiagnosis in the original cervical biopsy, an important subset were those diagnosed as high grade lesions on the cervical biopsy, but subsequently found to be low grade or benign lesions on cone biopsies.
excision. For this subset, it was also found that there was a decrease from 15.3% in 2005 to 13.4% in 2008 (highlighted in bold in Table III). In 2004-5, only 15 of 150 (10%) cases were reported by specialist gynaecological pathologists. In contrast, 123 of 149 (83%) cases were reported by specialist pathologists in 2008. The results show that for the cervical biopsies reported by general pathologists in 2004-2005, the incidences of consistent diagnosis, overdiagnosis and underdiagnosis were 68.1%, 17.0% and 14.8%, respectively. In contrast, for biopsies undergoing specialist reporting in 2008, the incidences of consistent diagnosis, overdiagnosis and underdiagnosis were 76.4%, 14.6% and 8.9%, respectively.

Tab. II. Number of consistent diagnoses between cervical biopsies and cones.

<table>
<thead>
<tr>
<th>Punch Biopsy Diagnosis</th>
<th>Cone Diagnosis</th>
<th>2004</th>
<th>% of total</th>
<th>2008</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>CIN1</td>
<td>5</td>
<td>3.3</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>CIN2</td>
<td>CIN2</td>
<td>45</td>
<td>30.0</td>
<td>70</td>
<td>47.0</td>
</tr>
<tr>
<td>CIN3</td>
<td>CIN3</td>
<td>35</td>
<td>23.3</td>
<td>27</td>
<td>18.1</td>
</tr>
<tr>
<td>INV</td>
<td>INV</td>
<td>5</td>
<td>3.3</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>CGIN</td>
<td>CGIN</td>
<td>3</td>
<td>2.0</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>NAD/INFL/META</td>
<td>NAD/INFL/META</td>
<td>3</td>
<td>2.0</td>
<td>5</td>
<td>3.4</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
<td>7</td>
<td>4.7</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>CIN 2/3</td>
<td>CGIN</td>
<td>(1)</td>
<td>(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGIN</td>
<td>CIN2/3</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>CIN(difficult to grade)</td>
<td>CIN2/3</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>CIN/INV</td>
<td>(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>103</td>
<td>68.7</td>
<td>113</td>
<td>75.8</td>
</tr>
</tbody>
</table>

NAD: No abnormality detected; INFL: Inflammation; META: Metaplasia; INV: Invasive carcinoma

Tab. III. Number of overdiagnoses in cervical biopsies compared with cones.

<table>
<thead>
<tr>
<th>Punch Biopsy Diagnosis</th>
<th>Cone Diagnosis</th>
<th>2004</th>
<th>% of total</th>
<th>2008</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2/3</td>
<td>CIN1</td>
<td>17</td>
<td>11.3</td>
<td>16</td>
<td>10.7</td>
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<tr>
<td>CIN2/3</td>
<td>HPV</td>
<td>3</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>CIN2/3</td>
<td>NAD/INFL/META</td>
<td>3</td>
<td>2.0</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>CIN3</td>
<td>CIN2</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>CIN1</td>
<td>HPV</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>CIN (difficult to grade)</td>
<td>HPV</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>CIN1</td>
<td>Atypia</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>25</td>
<td>16.7</td>
<td>22</td>
<td>14.8</td>
</tr>
</tbody>
</table>

NAD: No abnormality detected; INFL: Inflammation; META: Metaplasia; INV: Invasive carcinoma

Tab. IV. Number of underdiagnoses in cervical biopsies compared with cones.

<table>
<thead>
<tr>
<th>Punch Biopsy Diagnosis</th>
<th>Cone Diagnosis</th>
<th>2004</th>
<th>% of total</th>
<th>2008</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>CIN2/3</td>
<td>6</td>
<td>4.0</td>
<td>7</td>
<td>4.7</td>
</tr>
<tr>
<td>CIN2</td>
<td>CIN3</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>HPV</td>
<td>CIN (CIN1)</td>
<td>6</td>
<td>4.0</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>(CIN2/3)</td>
<td>(2)</td>
<td>(1)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CIN2/3)</td>
<td>(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN (CIN3)</td>
<td>INV</td>
<td>4</td>
<td>2.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>(CIN1)</td>
<td>(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CIN1)</td>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAD/INFL/META</td>
<td>CIN/INV</td>
<td>5</td>
<td>3.3</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>(INV)</td>
<td>(1)</td>
<td>(2)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CIN2/3)</td>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CIN1)</td>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAD/INFL/META</td>
<td>HPV</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Atypia</td>
<td></td>
<td>22</td>
<td>14.7</td>
<td>14</td>
<td>9.4</td>
</tr>
</tbody>
</table>

NAD: No abnormality detected; INFL: Inflammation; META: Metaplasia; INV: Invasive carcinoma
**Statistical analysis**

To determine if there was a difference in the incidence of over- and underdiagnosis between the two periods of reporting, Pearson’s chi-square test was applied. A statistically significant improvement in the rate of over-diagnosis was found (chi-square = 346, p = 0.03) and under-diagnosis (chi-square = 375, p < 0.01).

**Discussion**

Cervical punch biopsy is an essential component in cervical screening, yet it has limitations despite targeted sampling at colposcopy and care in specimen processing and reporting. A previous study showed that 33% of directed biopsies did not detect the high-grade lesion found in the cone, while 40% of random biopsies were able to detect high grade dysplasia. Assessment of cervical cone biopsies also has its challenges. In one study, 99 negative cones were reviewed and 21 cases were subsequently found to be positive for dysplasia or malignancy. In another study, 95 negative cone biopsies were subsequently found to have significant lesions. In this study, we investigated the accuracy of cervical punch biopsy reporting, as compared with subsequent diagnosis of cone excision specimens. We show that the rate of consistent diagnoses has increased from 2004 to 2008, from 68.7% to 75.8%. This was due to a statistically significant decrease in both the rates of over- and under-diagnoses. The reason for this improvement is most likely due to a change in the practice of reporting cervical biopsies, from that by general histopathologists in the general pool of specimens, to specialist reporting by gynaecological histopathologists, which was the only change in laboratory practice between both periods. In a previous study examining positive cones to determine the accuracy of biopsies, of 355 biopsy-proven cases of dysplasia, 323 had a subsequent positive cone. With 22 negative cones, the PPV was 91%. However, when only high grade lesions on pre-cone histology or cytology were analysed, 277 of 371 cases had a positive cone diagnosis, giving a sensitivity of 74.7%. Our current study therefore was comparable with a sensitivity of 89.7% and a PPV of 83.9% with specialist reporting.

Two other previous studies compared the consistency between the pre-cone diagnosis and the cone excision. The consistency rate between cervical biopsy and cone excision pathological diagnoses was 66.2% in one study and 63% in another. Our study showed a comparable consistency rate in the first period, but in the second period where specialist reporting was implemented, the rate was increased to over 75%.

It is important to note that in our cohort cases with under-diagnosis still underwent cone biopsies, although these diagnoses will not lead to a cone excision if considered in isolation. In these cases, the cone was performed on the basis of smear results of high grade dyskaryosis, persistent low grade dyskaryosis or a colposcopic impression of high grade lesion. This highlights the importance in which biopsy diagnoses are considered in context of the cervical smear and colposcopy results, thus leading to a cone excision despite a negative or low grade biopsy, if indicated.

The over-diagnosis rate is considered more critical, as it leads to cone excisions even if smear results and colposcopic impression are not consistent. In our study, the rate of over-diagnoses of high grade lesions was decreased from 15% to 13% from the first to the second period of study. This is significant, as cone excisions can be associated with complications (although rare), and hence should be avoided if not indicated.

It must be stated that the discrepancy between punch biopsy diagnosis and cone biopsy does not necessarily imply an incorrect interpretation by the pathologist in all cases. In some instances, the lesions are small and may be totally removed by the biopsy, and hence may not be represented in the subsequent cone. Also, although very informative and accurate in the majority of cases, cervical punch biopsies have their inherent limitations. It is possible that the biopsied part of the cervix at colposcopy does not target the area of actual abnormality, and hence the dysplasia is not detected due to an erroneous site of sampling. Improvements which may increase the accuracy of the biopsy include four quadrant biopsies and studying histological sections taken at multiple levels for thorough histological assessment. A fact that must also be acknowledged is that in some cases there is justifiable interobserver variability. Some biopsies are difficult to interpret due to being small, partially traumatised, poorly orientated or even showing very subtle changes that require much experience and may well initiate interobserver variability. Recent developments to improve the diagnosis of cervical biopsies, as well as cervical smears, include HPV genotyping for high risk HPV subtypes and immunohistochemistry for p16INK4a. These additional tests have been shown to aid in the diagnosis of CIN in equivocal and difficult cases. For example, p16INK4a has been shown to significantly improve the interobserver agreement between pathologists for punch biopsies.

**Conclusion**

In conclusion, the role of cervical biopsy is essential but still has its limitations. As recommended by the National Health Service (NHS) cervical screening programme, it is essential that patient management is based on co-ordinated information of smear results, history, colposcopy findings and cervical biopsy results. It is recommended that these specimens are reported by specialist gynaecological pathologists, which have been shown to be advantageous in increasing the diagnostic accuracy.
References


“Combined” desmoplastic melanoma of the vulva with poor clinical outcome

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Key words
Desmoplastic melanoma • “Combined” • Vulva • Immunohistochemistry • Protein S100

Introduction
Melanoma represents the second most frequent malignancy of the vulva. These neoplasms occur mostly in post-menopausal women and are generally diagnosed when they ulcerate and discharge blood. Vulvar desmoplastic melanomas are uncommon, and only a few cases have been documented. Herein, we report a case of “combined” desmoplastic melanoma.

Clinical history
A 73-year-old female sought medical attention for an ulcerated nodule of the right labia major. A biopsy was performed and a diagnosis of melanoma was rendered. Two weeks later she underwent surgical excision. The skin ellipse measured 2.5 × 2 cm and was centred by a grey ulcerated nodule measuring 2 cm in diameter. Sentinel lymph node procedure was performed and a right inguinal lymph node was removed. The sentinel lymph was metastatic. Completeinguinal lymphadenectomy failed to show other metastases. The patient died of widespread metastatic disease 3 years after diagnosis.

Materials and methods
The excised material was fixed in 10% formalin and embedded in paraffin. Deparaffinized 5-µm-thick sections were stained with haematoxylin and eosin. Immunohistochemistry was performed using the Ventana System employing the following antibodies: protein S100 (Ventana ready to use), MART-1 [Melan-A (A-103), Ventana ready to use], HMB-45 (Cell Marque ready to use), actin [muscle-specific (HHF35) Cell Marque ready to use].

Results
A 0.3 cm punch biopsy showed a hyperplastic epidermis with atypical melanocytes localized at the dermo-epidermal junction (Fig. 1). The upper dermis was infiltrated by epithelioid and pleomorphic melanocytes. Dilated capillaries reminiscent of Spitz lesion were also present (Fig. 2). The skin ellipse showed a polypoid, ulcerated and hypopigmented tumour (Fig. 3). The lesion was composed of single or grouped melanocytes, which reached the upper layer of the epidermis. In the deeper part of the dermis, the epithelioid component merged with spindle neoplastic cells interspersed among dense collagen bundles (Fig. 4) which represent-
Features of neurotropism and angiotropism were present. Protein S100 was ubiquitous (Fig. 5), while MART-1 strongly stained the epithelioid melanocytes of the spindle component of the upper part of the lesion that were almost negative in the desmoplastic areas except for rare spindle cells (Fig. 6), which were nonetheless faintly positive; HMB-45 stained only a few epithelioid melanocytes. Smooth muscle actin was negative.

The micro-staging of this lesion showed it to fall into the poor prognosis category (i.e. 5.7 mm in Breslow’s thickness, ulceration and the number of mitosis was at
at least 6 per mm²). The lymph node showed metastatic deposits composed of either spitzoid or desmoplastic areas (Fig 7).

Discussion

Desmoplastic melanoma (DM) is a rare variant of spindle cell melanoma that usually occurs in the sun-damaged skin of elderly patients. Conley et al. first described DM in 1971 as “a variant of spindle cell melanoma which elicits the production of abundant collagen” 5. Reed and Leonard further expanded the original description and documented the extensive infiltration or replacement nerve bundles typical of this melanoma subtype 6.

DM/neurotropic melanomas of the vulva are uncommon, and similar to mucosal melanomas, have a dismal prognosis 4. We report a case of “combined” DM of the labia minor consisting of a superficial spitzoid component and a deeper spindle desmoplastic component. S-100 expression was ubiquitous, while MART-1 and HMB-45 were limited to the superficial spitzoid component and were negative in desmoplastic areas. Notably, the nodal metastasis retained the same biphasic pattern seen in the primary tumour. This is infrequent considering that in a series of 55 DM only 2% showed lymph-node metastases 7. Complete lymphadenectomy failed to show other metastatic lymph nodes. The patient died 3 years later due to widespread metastases.

There is still controversy on the prognosis of DM. Early studies suggested an aggressive behaviour than conventional melanomas, while others documented DM with a more favourable clinical course 5. Busam et al. 8 suggested that pure desmoplastic melanomas thicker than 4 mm have a better prognosis when compared with combined DM and conventional melanomas of the same thickness. In their study, only 3 of 26 patients with pure DM died of disease compared to the experience of their institution, where 25% of patients died for thick conventional melanomas in 3 years. Our patient seems to confirm that thickness and the presence of “combined” histological components represent valuable prognostic indicators of poor outcome.

References

Tuberculosis is still one of the most frequent infectious diseases worldwide. Until the 1990s, Western European countries showed a low frequency of TB infection, but the rise of immigration has led to a rapid increase in its occurrence. In the elderly, TB is emerging as a significant health problem (age-related decline of the cell-mediated immunity, associated illnesses, use of immunosuppressive drugs, malnutrition, poor life conditions), although its detection and diagnosis is not easy also considering its subclinical presentation. Almost 70% of all TB infections in Italy are found in the lungs; 50% of the extrapulmonary infections affect lymph nodes. Due to the low incidence of superficial tuberculous lymphadenitis without pulmonary manifestations, the possibility of a TB aetiology is often not taken into consideration in the differential diagnosis of lymphadenopathy, resulting in significant delay of appropriate treatment.

Herein, we describe the case of a 78-year-old male with nocturnal fever, weakness, night sweats, loss of weight and decay in general condition. The patient had a past medical history of prostate adenocarcinoma treated with hormone therapy. The past medical history in association with clinical findings and laboratory data (anaemia, high titers of fibrinogen and reactive C-protein) led to the suspect of metastatic adenocarcinoma. Only histological and molecular biology findings allowed us to make a correct diagnosis of TB.

**Summary**

Tuberculosis (TB) is still one of the most frequent infectious diseases worldwide. According to the World Health Organization (WHO) 1, approximately one-third of the world’s population is currently infected with tubercle bacilli, while 8 million new cases of active disease develop each year and 3 million patients die 2. Until the 1990s, Western European countries showed a rather low frequency of TB infection, but the rise of immigration has led to a rapid increase in its occurrence 3. Furthermore, it is well known that TB can be associated with diseases that depress the immune system; such as leukaemia or HIV, affecting specific age groups (infants, elderly). In the elderly, TB is emerging as a significant health problem. It may be either exogenous or endogenous in origin, with the latter representing over 90% of cases and consisting of reactivation of dormant disease in the lungs or elsewhere in the body 4. Predisposing factors in the elderly are numerous. It is well known that the age-related decline of the cell-mediated immunity (thymus, lymph node and spleen involution) may cause reactivation of latent infections. Moreover, the presence of associated illnesses such as diabetes mellitus, chronic renal failure, diffuse parenchymal lung diseases, certain malignancies, as well as the use of immunosuppressive drugs (e.g. corticosteroids), may further impair cell-mediated immunity, increasing the risk of reactivation. Adverse social factors, such as malnutrition, poor living conditions as well as staying in nursing homes also affect the elderly much more frequently than younger individuals 4 5. In the former, TB is not easy to detect and diagnose because it does not manifest so clearly in these individuals. In fact, symptoms (loss of weight, night sweats, weakness, anorexia, mild fever) are often non-specific and may be attributed to age-related changes 6. The presence of other chronic diseases may confuse the clinical picture, and often the patient is unable to give an accurate account of symptoms.

**Introduction**

Tuberculosis (TB) is still one of the most frequently-occurring infectious diseases worldwide. According to the World Health Organization (WHO) 1, approximately one-third of the world’s population is currently infected with tubercle bacilli, while 8 million new cases of active disease develop each year and 3 million patients die 2. Until the 1990s, Western European countries showed a rather low frequency of TB infection, but the rise of immigration has led to a rapid increase in its occurrence 3. Furthermore, it is well known that TB can be associated with diseases that depress the immune system, such as leukaemia or HIV, affecting specific age groups (infants, elderly). In the elderly, TB is emerging as a significant health problem. It may be either exogenous or endogenous in origin, with the latter representing over 90% of cases and consisting of reactivation of dormant disease in the lungs or elsewhere in the body 4. Predisposing factors in the elderly are numerous. It is well known that the age-related decline of the cell-mediated immunity (thymus, lymph node and spleen involution) may cause reactivation of latent infections. Moreover, the presence of associated illnesses such as diabetes mellitus, chronic renal failure, diffuse parenchymal lung diseases, certain malignancies, as well as the use of immunosuppressive drugs (e.g. corticosteroids), may further impair cell-mediated immunity, increasing the risk of reactivation. Adverse social factors, such as malnutrition, poor living conditions as well as staying in nursing homes also affect the elderly much more frequently than younger individuals 4 5. In the former, TB is not easy to detect and diagnose because it does not manifest so clearly in these individuals. In fact, symptoms (loss of weight, night sweats, weakness, anorexia, mild fever) are often non-specific and may be attributed to age-related changes 6. The presence of other chronic diseases may confuse the clinical picture, and often the patient is unable to give an accurate account of symptoms.

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Apart from general diagnostic problems, there are difficulties regarding the recognition of TB affecting various sites. In fact, almost 70% of all TB infections in Italy are found in the lungs; of the remaining extrapulmonary infections, approximately 50% affect lymph nodes. Due to the low incidence of tuberculous lymphadenitis without pulmonary manifestations, the possibility of TB is often not taken into consideration in the differential diagnosis of lymphadenopathy, resulting in a significant delay of appropriate treatment.

Unfortunately, very little clinical data is available on the diagnosis and therapy of lymph node TB in Western countries. However, owing to the immigration that has taken place over the last decades, there is a renewed interest in the disease.

**Case report**

A 78-year-old male was admitted to the Geriatrics Unit of Catanzaro Hospital for the onset of nocturnal fever, weakness, night sweats, loss of weight and decay of general conditions, for a few weeks. The patient suffered from chronic obstructive airway disease and cerebral vasculopathy. Moreover, he had a history of prostatic adenocarcinoma treated with hormone therapy as well as a pacemaker. On physical examination, a swelling of a right laterocervical lymph node was observed. In particular, the node was tender, mobile and painful with irregular borders. Blood pressure was 110/60 mmHg, heart rate 94 beats per min (bpm) and body temperature was 38.1°C. Laboratory data revealed hyperleucocytosis ($5.9 \times 10^3$/mm$^3$) with absolute neutrophilia (neutrophils 78.3%, lymphocytes 13.3%), normochromic normocytic anaemia (haemoglobin 10.5 g/dl, mean corpuscular volume 88 μm$^3$) with an increase of acute phase proteins (C-reactive protein-PCR, procalcitonin, fibrinogen). To rule out a metastatic adenocarcinoma of the prostate or lymphoproliferative disorder, a lymph node ultrasound imaging (US) of the neck and a whole body CT-scan were performed. The US revealed an enlarged (7 cm in maximum diameter), inhomogeneous lymph node with a hyperechoic centre, and on this basis, tubercu-
lous lymphadenopathy was suspected. Shortly after, a Mendel-Mantoux test as well as sputum and urinalysis were carried out with negative results.

Histological and microbiological analyses of the lymph node were also conducted by US-guided fine-needle aspiration (FNA). One aliquot of FNA sample was fixed in 95% ethyl alcohol and stained by Giemsa for cytologic analysis. Immunohistochemistry for CKAE1/AE3 and PSA was made. Another aliquot was used for microscopic detection of the microorganism using Ziehl-Neelsen (ZN) stain as well as agar and radioactive culture (BACTEC). To assess the genotype of the mycobacterium, polymerase chain reaction (PCR) and the IS6110 restriction-fragment-length-polymorphism (RFPL) were performed using standard methods 9.

Lymph node architecture was effaced by the presence of large granulomas, sometimes confluent, with central necrosis (Fig. 1a). A number of epithelioid cells (arranged in a palisaded architecture), multinucleated giant cells of Langhans type and, occasionally, foreign body type in between, encircling caseosis and bordered by lymphocytes and plasma cells, were surrounded by thick fibrous layers (Fig. 1b). CKAE1/AE3 and PSA were negative. ZN and PCR for mycobacterium tuberculosis were positive (Fig. 1c-d). On the basis of the morphological and molecular biology findings, a diagnosis of tuberculous lymphadenopathy was made.

Treatment with isoniazid, rifampicin and pyrazinamide was established, according to the recommendations of the American Thoracic Society 10, with immediate improvement of clinical conditions. One month later, the patient developed hepatotoxicity, and isoniazid and rifampicin was replaced with rifabutin.

Discussion

TB remains one of the leading infectious diseases, causing significant morbidity and mortality worldwide 11. Although the reporting of new TB infections has declined steadily over time, the frequency of lymph node TB has not decreased and accounts for almost 7.5% of all patients infected by mycobacterium tuberculosis. Nevertheless, it seems that tuberculous lymphadenopathy is not taken into consideration in Western countries and diagnosis is performed only by histological examination 12.

In the present case, the past medical history (prostatic adenocarcinoma), in association with clinical findings (fever associated with vague and non-specific symptoms) and laboratory data (anaemia, high titres of fibrinogen and PCR) led to the suspect of metastatic adenocarcinoma. Only histological and molecular biology findings allowed us to make a correct diagnosis. Differential diagnosis of granulomatous lymphadenopathy includes sarcoidosis (well-defined, non-caseating granulomas with a ring of collagen), atypical mycobacterial infections (less granulomatous changes with more acute inflammation, sometimes with abscess formation and a histiocytic proliferation of spindle cells mimicking an inflammatory pseudotumor), lepromatous leprophediasis (rare, non-caseating granulomas with numerous foamy macrophages replacing the paracortical regions and containing abundant intracellular organisms) and Hodgkin lymphoma (non caseating granulomas in the paracortical areas, Reed-Stember and Hodgkin cells).

Conclusion

It is important to bear in mind that TB infection, although infrequent, may be the cause of a lymphadenopathy. In elderly patients, a delay in diagnosis represents a serious problem since TB is curable only when treatment is established at an early stage 4.

The pathological examination of lymph nodes plays a critical role in diagnosis. In fact, although from a clinical viewpoint there may be some confusion as to whether an enlarged lymph node is due to TB or to other benign or malignant lymphadenopathies, the histological picture is characteristic and diagnosis is readily established by biopsy examination of the lymph node. Moreover, the demonstration of Koch’s bacillus using Ziehl-Neelsen stain and PRC is definitive.

References

CASE REPORT

Adenolipoma of the skin

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Key words

Adenolipoma • Perisudoral lipoma • Eccrine glands • Lipoma • Skin

Summary

Adenolipoma of the skin (ALS) is an uncommon histological variant of lipoma, characterized by the presence of normal eccrine sweat glands inside the fat proliferation. A 32-year-old woman presented to our department with a slow-growing, painless subcutaneous soft tumour located on the upper part of the right thigh. Microscopically, there was lobulated adipose tissue proliferation with well-differentiated eccrine glands and ducts in the periphery and centre of the nodule. These features were suggestive of ALS. ALS is a rare microscopic variant of cutaneous lipoma having similar clinical features to lipoma. The most frequent locations of this tumour are thighs (as in our patient), shoulders, chest and arms. Histologically, the tumour is composed of lobulated adipose tissue with larger and more prominent lobules than those in normal subcutaneous adipose tissue. A well-developed capsule may also be identified. Eccrine glands and ducts, without proliferative changes, are well-differentiated within the adipose tissue. Differential diagnosis of adenolipoma includes the common lipoma and its variants, skin tag and other hamartomatous lesions, such as nevus lipomatosus superficialis, and the lipomatous variant of eccrine angiomatous hamartoma.

Introduction

Adenolipoma of the skin (ALS) is an uncommon histological variant of lipoma characterized by the presence of normal eccrine sweat glands inside a fat proliferation. We report a new case with a review the literature.

Case report

A 32-year-old woman presented to our department with a slow-growing, painless nodule on her thigh. Cutaneous examination showed a subcutaneous soft tumour of 1.5 cm in diameter located on the upper part of the right thigh. The lesion was covered by an erythematous skin, with no palpable thrill (Fig. 1). A diagnosis of lipoma was suspected. Surgical excision of the tumour and the overlying skin was performed.

Gross examination revealed a soft, yellow, lobulated mass measuring 3 cm in greatest diameter. Microscopically, the nodule was composed of adipose tissue proliferation with distinct lobulation within the tumour. Well-differentiated eccrine glands and ducts were seen in the periphery and centre of the nodule. No capsule was seen and no architectural or cytological alteration was noticed in these glands (Fig 2). These features were suggestive of ALS.

Discussion

Several variants of lipoma were described according to their location and morphology. In a lipoma, the adipose tissue may be associated with other proliferative or non-proliferative tissues, such as in angiolipoma and fibrolipoma

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In 1993, Hitchcock et al. described an entity of lipoma in a series of 9 patients that had never been reported previously. It was a rare microscopic variant of cutaneous lipoma composed of large lobules of mature adipocytic tissue admixed with eccrine ducts and glands. This tumour was called “adenolipoma of the skin” 2.

Ait-Ourhrouil and Grosshans reported, in 1997, a second series of 11 cases 3. They postulated that this lesion develops from the peripheral adipose tissue of eccrine glands and suggested the name perisudoral lipoma. Including our patient, the total number of ALS reported cases, in the English and French literature is 31 (Tab. I) 2-10. The tumour often has the appearance of a usual lipoma. Occasionally, the clinical presentation is suggestive of skin tag, neurofibroma or a hamartomatous lesion. The delay between tumour occurrence and the first medical evaluation ranges from 6 months (in our case) to more than 10 years 3,5. The average size calculated from our literature review is 2.7 cm 2-10. There is a female preponderance (22:9), and the average age at diagnosis is 47.8 years 2-10. ALS is mainly located on the thigh (especially its upper part) and buttock (n = 16). The other reported locations are: the shoulder region (n = 3), abdomen (n = 2), periangual region (n = 2), female external genitalia (n = 2), axillary region (n = 1), lower lip (n = 1), supraclavicular region (n = 1), arm (n = 1), hip (n = 1) and breast (n = 1) 2-10.

Histologically, the tumour is composed of lobulated adipose tissue with larger and more prominent lobules than those in normal subcutaneous adipose tissue. Unlike our patient, a well-developed capsule may also be identified. Eccrine glands and ducts, without proliferative changes, are well-differentiated within adipose tissue 2,3. Only one case of ALS with apocrine glandular cystic component has been reported in a 40-year-old female patient with an axillary tumour 4.

The frequency of adenolipoma might be underestimated, especially when sectioning of lesions can miss the few glandular components or when it is impossible to precisely locate eccrine glands within fragmented specimens. When the eccrine glands have a peripheral location in specimens, it may be also difficult to affirm whether the glands are within the tumour or are contained in adjacent normal structures 2,4.

The histological differential diagnosis of adenolipoma includes common lipoma and its variants, skin tag, also in addition to other hamartomatous lesions, such as nevus lipomatosus superficialis and the lipomatous variant of eccrine angiomatous hamartoma 11-12. Adenolipoma usually has a similar clinical presentation to common lipoma. The size of adenolipoma appears to be smaller than that of common lipomas, probably because of its superficial location that can lead to earlier symptoms. A subcutaneous lipoma may have a herniation within the dermis. In this latter case, the eccrine glands are compressed and displaced rather than incorporated into the lesion as in ALS 2.

Skin tag with a fatty stroma is also a differential diagnosis. In this tumour, the eccrine glands are rather located on both sides of the pedicle rather than within the fatty component 3.

Nevus lipomatosus superficialis has a different clinical feature. It presents as congenital multiple papules or nodules. Microscopically, it shows ectopic adipose tissue with fibrous tissue in the papillary and reticular dermis. The density of the collagen bundles, the abundance of fibroblasts and its vascularity are more prominent than in normal skin 2,11.

Eccrine angiomatous hamartoma is usually an isolated congenital lesion showing a preponderance of eccrine and vascular proliferation, which are absent in ALS 2,12. ALS is a fatty-tissue proliferation that includes and moves the normal eccrine glands to the centre of the tumour. This glandular component does not show any proliferative changes. Its location on the upper thigh, as in our patient, may allow clinical suspicion of ALS which should be confirmed by histological findings.
References


Tab. I. Summary of the reported cases of ALS.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Location</th>
<th>Size</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Hitchcock 1993</td>
<td>25</td>
<td>M</td>
<td>Arm</td>
<td>1 cm</td>
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</tr>
<tr>
<td></td>
<td>61</td>
<td>M</td>
<td>Thigh</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>F</td>
<td>Shoulder</td>
<td>6 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>F</td>
<td>Supravcicular</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>M</td>
<td>Shoulder</td>
<td>4 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>F</td>
<td>Thigh</td>
<td>0.8 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>F</td>
<td>Thigh</td>
<td>1.5 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>F</td>
<td>Thigh</td>
<td>4.4 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>M</td>
<td>Thigh</td>
<td>4 cm</td>
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<td>Ait-Ourhrouil 1997</td>
<td>63</td>
<td>F</td>
<td>Thigh</td>
<td>1 to 3 cm</td>
<td>&gt; 10 years</td>
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<tr>
<td></td>
<td>55</td>
<td>M</td>
<td>Shoulder</td>
<td>5 years</td>
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<tr>
<td></td>
<td>71</td>
<td>M</td>
<td>Abdomen</td>
<td>&gt; 10 years</td>
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<td></td>
<td>61</td>
<td>F</td>
<td>Buttock</td>
<td>2 years</td>
<td></td>
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<tr>
<td></td>
<td>44</td>
<td>F</td>
<td>Buttock</td>
<td>Many years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>F</td>
<td>Hip</td>
<td>Many years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>M</td>
<td>Thigh</td>
<td>2 years</td>
<td></td>
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<td></td>
<td>63</td>
<td>F</td>
<td>Breast</td>
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<tr>
<td></td>
<td>48</td>
<td>F</td>
<td>Thigh</td>
<td>Many years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>F</td>
<td>Thigh</td>
<td>Many years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
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<td>Abdomen</td>
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<tr>
<td>Rongioletti 1997</td>
<td>41</td>
<td>F</td>
<td>Thigh</td>
<td>2.7 cm</td>
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</tr>
<tr>
<td></td>
<td>25</td>
<td>F</td>
<td>Thigh</td>
<td>2 cm</td>
<td>5 years</td>
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<tr>
<td>Chadli-Debbiche 2001</td>
<td>34</td>
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<td>Thigh</td>
<td>8 cm</td>
<td>11 years</td>
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<tr>
<td>Ide 2003</td>
<td>57</td>
<td>F</td>
<td>Lower lip</td>
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<td>3 years</td>
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<td>Many years</td>
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<tr>
<td></td>
<td>48</td>
<td>M</td>
<td>Periungual (great toe)</td>
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</tr>
<tr>
<td>Del Agua 2004</td>
<td>45</td>
<td>F</td>
<td>Thigh</td>
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<td>Antunez 2005</td>
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<td>Axillary region</td>
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<tr>
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<td>F</td>
<td>Left groin</td>
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<td>Many years</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>F</td>
<td>Right vulva</td>
<td>2 cm</td>
<td>4 years</td>
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<tr>
<td>Present case</td>
<td>32</td>
<td>F</td>
<td>Upper thigh</td>
<td>3 cm</td>
<td>6 months</td>
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</tbody>
</table>

Note: N/A = Not available.
Adenomatous transformation in a giant solitary Peutz-Jeghers-type hamartomatous polyp

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Key words
Peutz-Jeghers-type polyp • Hamartoma • Adenomatous transformation • Rectum

Summary
Introduction
Solitary Peutz-Jeghers-type polyps (PJP) are uncommon hamartomatous lesions without associated mucocutaneous pigmentation or a family history of Peutz-Jeghers Syndrome (PJS)\(^1\)\(^2\). They are most frequently encountered in the small intestine, but rarely involve the rectum. Although several cases of solitary PJP have been reported in the literature, it is still unclear whether solitary PJP represents an incomplete form of PJS or a different entity\(^3\). In this paper, the authors report a new case of solitary Peutz-Jeghers-type hamartomatous polyp with several foci of glandular dysplasia revealed by rectal bleeding. To the best of our knowledge, only 31 cases (Tab. I) of colorectal solitary Peutz-Jeghers-type hamartomatous polyps have been published in the English language literature to date, and adenomatous transformation has never been described in solitary rectal PJP before.

Clinical history
A 27-year-old previously healthy female patient with no family history of gastrointestinal polyposis, presented with a two-month history of rectal bleeding. On examination, the patient’s skin including the perioral area was unremarkable and oral mucosa appeared normal. Endoscopic examination revealed a solitary lobular polyloid lesion in the lower rectum. The polyp was sessile and measured 15 cm in diameter. As histological examination of the biopsy specimen was suggestive of adenoma, endoscopic polypectomy was performed. Histologically, this polyp had an arborizing muscular network originating from the muscularis mucosa, and was covered by well organized mucosa with several foci of dysplastic glands. The final pathological diagnosis was solitary Peutz-Jeghers type hamartomatous polyp with adenomatous transformation.

Discussion
A Peutz-Jeghers polyp (PJP) in a patient without mucocutaneous pigmentation or family history of PJS is called...
an isolated or solitary PJP. Whenever a PJP is found, it is important to rule out a diagnosis of PJS on the basis of WHO criteria: (1) three or more histologically confirmed PJP; (2) any number of PJP with a family history of PJS; (3) characteristic, prominent, mucocutaneous pigments with a family history of PJS; (4) any number of PJP and characteristic, prominent, mucocutaneous pigmentation. In our case, histological examination showed the characteristic features of PJP, but the patient did not fulfill WHO criteria for PJS diagnosis (negative family history for PJS and absence of mucocutaneous pigmentation), and was therefore considered to have a solitary PJP. Solitary Peutz-Jeghers polyps are extremely rare, with an estimated incidence of 1:120,000. They are found most frequently in the small intestine, but also occur in the large bowel and stomach. A Medline search of the English language literature revealed only three well-documented cases of solitary Peutz-Jeghers-

Fig. 1. Endoscopic examination revealing a lobular rectal polyp.

Fig. 2. Arborizing network of smooth muscle and connective tissue surrounding abundant normal glands. (haematoxylin & eosin; original magnification x 10).

Fig. 3. Cystically dilated glands were identified within the polyp. (haematoxylin & eosin; original magnification x 25).

Fig. 4. Hyperplastic glands composed of tall columnar absorptive cells and goblet cells. (haematoxylin & eosin; original magnification x 25).

Fig. 5. Foci of dysplastic glands were noticed within the polyp. (haematoxylin & eosin; original magnification x 25).
f. limaiem et al.

The largest colorectal PJP reported in literature had a size of 2.5 cm compared to 15 cm in our patient. Gastrointestinal hamartomatous polyps in patients with PJS have a distinct histological appearance with interdigitating smooth muscle fibres forming a characteristic branching tree pattern (arborization) \(^8\). They display a frond-like elongated epithelial component and cystic gland dilatation extending into the sub-mucosa or muscularis propria. Peutz-Jeghers-type polyps are histologically identical to those in Peutz-Jeghers syndrome, although some authors have pointed out that solitary Peutz-Jeghers-type polyps tend to exhibit less branching of the muscularis mucosae than in the familial form \(^9\) \(^10\).

The main difficulty in defining the true entity of these solitary hamartomatous polyps lies in the small number of published cases, some of which provide little clinical information. Because of the absence of involved family members, the lack of muco-cutaneous pigmentation characteristic of PJS and the presence of a solitary polyp, a solitary PJP might be a disease entity distinct from PJS. There is, however, controversy about the occurrence of solitary PJPs \(^1\) \(^5\). In most case reports and series, clinical and histological criteria were not fully documented and there was usually no extended follow-up \(^11\). Hamartomatous polyps are generally considered to have very low malignant potential \(^11\). However, some reports have described areas of neoplastic change, such as adenomatous or carcinomatous change in solitary PJP \(^9\) \(^12\)-\(^14\). Patients with PJS are at increased risk of developing both intestinal and extraintestinal malignancies. Since solitary PJP are rare, it is not known whether there is any increased risk for other malignancies, as observed in PJS. In 50–94% of patients with PJS, a mutation of the LKB1/STK11 gene is found. Conversely, no mutation of the LKB1/STK11 gene was found in two cases of solitary PJP in which genotyping was carried out \(^15\) \(^16\). Unfortunately, we were not able to carry out genotyping in our case.

In summary, a case of solitary Peutz-Jeghers-type polyp with adenomatous transformation is reported herein. Our case is unique in that it is the largest solitary PJP reported in literature involving the rectum which is an exceedingly rare location. It is still unclear whether a solitary Peutz-Jeghers polyp (PJP) is an incomplete form of PJS or a separate entity. Whether there is an increased risk of cancer in patients with solitary Peutz-Jeghers-type polyps is uncertain, but periodic surveillance in young patients would seem appropriate \(^4\). Available data are extremely limited, and it is difficult to draw firm conclusions regarding management of patients with solitary polyps \(^5\).

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**Tab. I.** Cases of colorectal solitary Peutz-Jeghers type polyps reported in the literature.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Number of cases</th>
<th>Age (years)</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suda (^17) (1988)</td>
<td>20</td>
<td>Mean age = 55.1 years Males: 74%</td>
<td>Colorectal</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Handa (^13) (1990)</td>
<td>1</td>
<td>NA</td>
<td>Colon</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yamanaka (^18) (1991)</td>
<td>1</td>
<td>NA</td>
<td>Transverse colon</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Muto (^9) (1993)</td>
<td>1</td>
<td>NA</td>
<td>Colon</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nakayama (^19) (1996)</td>
<td>1</td>
<td>64/M</td>
<td>Lower rectum</td>
<td>2x1.5 x 1.5</td>
<td>Bloody stools</td>
<td>Transanal surgical resection</td>
</tr>
<tr>
<td>Oncel (^4) (2003)</td>
<td>5</td>
<td>46/M</td>
<td>Sigmoid</td>
<td>1.5</td>
<td>Screening</td>
<td>Endoscopic polypectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68/M</td>
<td>Sigmoid</td>
<td>2.5</td>
<td>Screening</td>
<td>Endoscopic polypectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46/M</td>
<td>Sigmoid</td>
<td>2</td>
<td>Screening</td>
<td>Endoscopic polypectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33/F</td>
<td>Sigmoid</td>
<td>2</td>
<td>Rectal bleeding</td>
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<tr>
<td></td>
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<td>56/M</td>
<td>Cecum</td>
<td>2</td>
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<td>Jaremko (^19) (2005)</td>
<td>1</td>
<td>19/M</td>
<td>Descending colon</td>
<td>NA</td>
<td>Colo-colonic intussusception</td>
<td>Subtotal colectomy</td>
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<td>50/M</td>
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<td>1.8</td>
<td>Screening</td>
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<tr>
<td>Garces (^21) (2011)</td>
<td>1</td>
<td>NA</td>
<td>Rectum</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Limaiem (2011)</td>
<td>1</td>
<td>27/F</td>
<td>Lower rectum</td>
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Il sito her2testing.it si arricchisce di una nuova e importante sezione interamente dedicata alla corretta determinazione dello stato di HER2 nel carcinoma mammario.

Una sezione accessibile sempre dal sito www.her2testing.it che fornirà al patologo contenuti e risorse utili dedicate all’esecuzione e interpretazione del test HER2 nel carcinoma mammario, con le sue specifiche caratteristiche e differenze rispetto al carcinoma gastrico.

Una serie di contenuti formativi e interattivi che aiuteranno il patologo ad approfondire la letteratura scientifica di riferimento e le linee guida nazionali e internazionali, e perfezionare la pratica clinica.

La struttura del sito consentirà al patologo di avere accesso alle sezioni teoriche e pratiche che, come per la sezione dedicata al carcinoma gastrico e della giunzione gastroesofagea, saranno divise in:

✔ **Area formazione su HER2** sezione dedicata alla pratica clinica, con esercizi interattivi sull’assegnazione dello score HER2 e gli interventi audio video della rubrica Incontra l’esperto, con testimonianze degli esperti membri del Board scientifico.

✔ **Saperne di più su HER2** sezione dedicata all’approfondimento della teoria, contenente guide illustrate, filmati con i commenti degli Opinion leader internazionali di riferimento, le pubblicazioni fondamentali della letteratura scientifica nazionale e internazionale.

Anche per questa nuova sezione dedicata al carcinoma mammario sono previsti aggiornamenti periodici e costanti per garantire al patologo la possibilità di avere a disposizione un sito sempre più ricco di contenuti e risorse utili alla pratica clinica.

La sezione dedicata al carcinoma gastrico e della giunzione gastroesofagea è sempre attiva e a disposizione del patologo e si arricchisce di nuovi e interessanti aggiornamenti.

Oltre alla nuove letture ed esercitazioni che vanno ad implementare le sezioni **Area formazione su HER2** e **Saperne di più su HER2** sono disponibili su HER2:

✔ **Un link diretto per accedere alla FAD HER2 nel carcinoma gastrico e della giunzione gastroesofagea**

✔ **News da Congressi e Webcast**: è stato pubblicato nella sezione dedicata agli appuntamenti congressuali il webcast del Simposio Medicina personalizzata: dalla malattia HER2 positiva al melanoma che si è svolto a il 28 ottobre 2011 a Palermo durante l’ultimo Congresso Siapec
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