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Histological evaluation of papillary lesions of the breast from needle biopsy to the excised specimen: a single institutional experience
S. Giliani, R. Tashjian, P. Kowalski

Background. The assessment and categorization of papillary lesions remains one of the most challenging areas in breast pathology. We evaluated the histological follow-up of papillary lesions of the breast from needle core biopsy to final excision to determine whether these lesions warrant excision, irrespective of histological subtype.

Study Design. A total of 91 needle core biopsies from the breast diagnosed as “papillary lesions” at our institution from January 2001 to June 2011 were included in the study. Twenty-nine of these (mean patient age 54.93 ± 12.5 SD) were reported as benign papillary lesions, and the remaining 62 (mean patient age 61.98 ± 15.20 SD) were diagnosed as either atypical papillary lesions (17 cases) or malignant papillary lesions (45 cases).

Results. Of the 29 needle core biopsies reported as benign, 19 cases (65.5%) were diagnosed as benign and three (10.3%) were diagnosed as malignant on follow-up. The remaining seven cases did not proceed to excision. Sixty-two of the 91 cases were given a diagnosis of either atypical papillary lesion or malignant papillary lesion on needle core biopsy. Of the 45 cases initially diagnosed as malignant, 44 (97.7%) were eventually deemed malignant and one atypical ductal hyperplasia (ADH) was found upon excision. The initial diagnosis of atypical papillary lesion was rendered in 17 cases, of which 10 turned out to be malignant, five ADH, and two benign on excision.

Conclusion. We conclude that if a benign papillary lesion is present on initial needle biopsy, then the probability of malignancy is high (10.3%) on the final excision. Similarly, all malignant papillary lesions diagnosed on needle core biopsy should be excised due to the very high likelihood (97.7%) of a diagnosis of malignancy on final excision. Based on our results, we suggest surgical excision of any papillary lesion diagnosed on needle core biopsy.

Case reports
Pancreatic adenocarcinoma in duodenal ectopic pancreas: a case report and review of the literature
A. Ginori, L. Vassallo, M.A.G.M. Butorano, F. Bettarini, G. Di Mare, D. Marrelli

Ectopic pancreas is defined as pancreatic tissue outside the normal location without connection to the normal pancreas. It occurs throughout the gastrointestinal tract, most commonly in the stomach (25-60%), followed by the duodenum (25-35%) and jejunum (16%). It may develop the same pathological changes of a normal pancreas such as acute pancreatitis and cyst formation. Malignant degeneration rarely occurs. We present a case of heterotopic pancreatic adenocarcinoma localized in the duodenal bulb presenting with symptoms of gastric obstruction.

Pulse granuloma involving Meckel’s diverticulum: a case report and literature review
J.K. Karp, A. Davis, P.J. Read, A. Mashayekh, A. Bombonati, F. Palazzo

Pulse granuloma is a rare, benign entity that most likely represents a reaction to vegetable material and is characterized by hyaline rings and foreign-body giant cells. We report a case of a pulse granuloma involving Meckel’s diverticulum. The patient presented with abdominal pain and radiological findings consistent with Meckel’s diverticulum. Microscopic examination of the resected tissue confirmed diagnosis of Meckel’s diverticulum with small bowel mucosa. Peridiverticular foreign-body giant cells, hyaline rings and circular structures containing calcified basophilic granules were also identified, consistent with pulse granuloma. Pulse granulomas have been reported in a variety of locations, most commonly in the oral cavity. To the best of our knowledge, this is the first reported example of pulse granuloma in Meckel’s diverticulum. Familiarity with pulse granuloma allows for the timely and accurate diagnosis of this entity, particularly in sites not previously described in the literature.

Sclerosing stromal tumour of the ovary: two case reports
F. Limaiem, E. Boudabous, S. Ben Slama, B. Chelly, A. Lahmar, S. Bouraoui, F. Gara, S. Mzabi

Sclerosing stromal tumours are rare benign ovarian neoplasms of the sex cord stromal that occur predominantly in the second and third decades of life. Herein, we report two cases of sclerosing stromal tumour of the ovary. The two patients were 16 and 45 years old and both presented with pelvic pain. Ultrasonography demonstrated a heterogeneous solid mass of the left and right ovary, respectively, with some cystic foci in the second tumour. Laboratory tests including tumour markers and serum hormonal assays were normal in both cases. The two patients underwent left and right salpingo-oophrectomy, respectively. Microscopically, the tumours showed a pseudolobular pattern with cellular areas separated by oedematous and collagenous areas. The cellular areas were richly vascularized, with a hemangiopericytic pattern, and were composed of an admixture of theca-like and spindle-shaped cells. Immunohistochemical studies showed that the tumour cells were positive for smooth muscle actin, inhibin and vimentin, but negative for cytokeratin. The final pathological diagnosis was sclerosing stromal tumour. Postoperative course was uneventful for both patients.

Diagnosis and clinical course of cardiac myxoma
M. Mlika, A. Ben Youssef, R. Hamrouni, A. Ayadi-Kaddour, T. Kilani, F. El Mezni

Cardiac myxomas are the most common benign tumours of the heart. In spite of their benign nature, these tumours may induce metastasis or recurrences. Their diagnosis is challenging because of the lack of specific signs, and positive diagnosis is based on microscopic findings. We report a case series of 6 patients documented by radiologic and microscopic findings. In addition, one case was unique due to its location in the right atrium. Tumours were detected by trans-oesophageal ultrasound examination in all cases. They were located in the left atrium in five cases and in
the right side in one case. All patients underwent a successful surgical excision with en-bloc removal of the tumour. The outcome was fatal in one patient because of atrial arrhythmia.

**Lung metastasis from TTF-1 positive sigmoid adenocarcinoma. Pitfalls and management**


The lung is a frequent site of metastatic involvement, and in many cases the differential diagnosis between a metastasis and a primary carcinoma is a substantial question. TTF-1 is considered as a reliable marker for differential diagnosis in distinguishing primary lung carcinoma and metastasis, especially when dealing with an adenocarcinoma or a large-cell carcinoma. It was generally thought that adenocarcinomas arising in the gastrointestinal tract do not express TTF-1. Recently, it has been reported that a small percentage (1.8%-5.8%) of intestinal adenocarcinoma TTF-1 positive show differences in sensitivity/specificity depending on the antibody clones. We report a case of lung localization of a TTF-1 positive adenocarcinoma in a patient with a history of colon adenocarcinoma. Based on the current results and previous reports, we propose the following criteria for diagnosing lung metastasis from TTF-1 positive intestinal adenocarcinoma. 1) Clinical features and anamnestic history are diagnostic milestones, and provide very important information as a prognostic parameter of primary carcinoma and the time interval between the two localizations (primary and metastasis). 2) The histologic features are compatible with an enteric differentiation. 3) TTF-1 must be tested in the primary carcinoma. 4) In lung lesions, in association with TTF-1, it could be useful to test other immunohistochemical markers such as CDX-2 and NapsinA. 5) Testing other immunohistochemical or molecular markers in either lesion is not very useful. Heterogeneity between primary and metastatic lesions has been reported in the literature. Application of the above-mentioned criteria would simplify diagnosis of lung metastases from TTF-1 positive intestinal adenocarcinoma.

**Primary tuberculosis of the adenoids in an 11-year-old male presenting with hearing loss: a case report**

* S. Taghipour-Zahir, M.H. Baradaranfar, A.A. Zolfaghari

Hypertrophy of adenoids is usually caused by repeated throat infections, especially viral and bacterial infections, that in microscopic examination reveal reactive lymphoid follicular hyperplasia. Herein, we present an 11-year-old boy who developed hearing loss in his left ear three months before admission, and in direct examination the adenoids were hypertrophied. Histopathological study of the resected adenoid revealed caseating granulomatous inflammation. Based on histopathological and clinical findings, primary tuberculosis of adenoids was suggested which was confirmed by PCR.
On the question of cognitive limits in diagnostic histopathology

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Key words
Diagnostic histopathology • Cognitive process • Immunohistochemistry • Tables of truth

Summary

From a solely morphological point of view, histopathological diagnosis is subject to interpretation variables that may be investigated from an epistemological aspect. On the basis of the most suitable ways of approach, the authors examine some theoretical aspects involved in writing a histopathological report. In particular, the following are considered: problems regarding the perception of shapes, induction, deduction, abduction and some aspects of formal logic connected with the evaluation of immunohistochemical investigations. The main reasons for diagnostic mistakes are underlined, and the opportunity for an awareness of the logical and mental mechanisms involved in the evaluation of morphological data is outlined.

The operative context of diagnostic histopathology, on one hand, above all in relation to the approach proceeding the methods of biopsies and needle-aspirated cytology, and on the other hand the application of – by now routine – ancillary methodologies, such as immunohistochemistry, presents difficulties linked with its own procedural nature, among which:

- the relationship with clinicians, above all oncologists, who, seeking stricter and stricter conventional parameters, aim at achieving absolute objectivity of a diagnostic definition which is nonetheless conditioned to correspond with codifications previously established regardless of morphology;
- the difficulty in justifying, under the procedural aspect, both from anatomo-clinical and medical-forensic points of view, the often incomplete understanding of a pathological picture which seldom falls completely within a pre-set scheme;
- the complexity inherent in having to translate the interpretation of a datum (a tissue fragment), supposed to be evident by itself, into a predictive diagnostic option of future biological behaviour, which is often difficult to identify through ordinary acquisitions.
In the last analysis, diagnostic variability exists and it can be tracked down, among various occurrences, to subjectivity in the interpretation of morphological pictures, to the existence of diagnostic criteria at times slightly defined or barely reproducible, to the presence of border lesions with a thin dividing line between benign and malignant, to the rarity of some pathologies and/or the precociousness of their identification. The aim of the present study is to emphasize some methodological assumptions that are involved in the complexity of the diagnostic act in histopathology. This, obviously, without getting deeper into the exquisitely subtler logico-philosophical questions linked to the use of the terms considered, the sole aim to emphasize the possibility of working through an experience at a different level of understanding.
If, then, morphology, failing a real specificity of form, does not allow grasping the real nature of a lesion, if not in an approximate way; if language does not offer “clear and distinct” expressions and shared terms able to describe perceived reality in a univocal way and if, in its turn, perception can present oscillations in the Gestalt organization of data, the evidence of the object, in the practice of histopathological diagnostics, risks shading on the ground of indeterminateness.
It would, then, be necessary to seek a more rigorous definition of our relationship with reality or, anyway, of the conditions and the ways through which we get to know it.

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We must wonder and ascertain when – in relation to which reasoning – our diagnoses may be true, probable or just hypothetical; if it is always possible to diagnose every lesion correctly; if morphological criteria are, in this regard, strict enough; which variables may modify our perceptive aptitude; which cognitive approach can guarantee the lowest possible rate of error.

It is, then, a question of attaining the correspondence between the perceptive data with a conceptualization to express in a (single) term – as rich as possible with information and the least generic as possible – which is communicable, reproducible and distinguishable within a nosological spectrum that is coherent with the pathogenesis and biological behaviour of the lesion.

Pizzi states: «It does not make sense to ask an observer, “What can you see through the microscope?”, because nobody can describe in a finite time what one can see in a given moment. The idea that a neutral observer – working as a perfectly passive camera – may exist is an empiricist myth. We make observations to answer problems posed to us and such questions depend on the theory we are testing».

Even being able to often draw different hypotheses and/ or different interpretations from tissue analyses, and even being aware that truth represents a wider context than demonstrability, the aim, at a diagnostic level, is always to reach the truth, an essential condition to guarantee an actual benefit to the patient.

As far as the question of truth is concerned, the transition from ontology (what is the essence of the object of knowledge?) to epistemology (how do I know the object?) seems, at present, a way with no return. Truth becomes, in this way, accessible as long as we have a suitable method: the subject comes to play a prevailing role in relation to the object.

Now, the first experience of a pathologist in front of a histological specimen is a perceptive experience.

By selecting the perceived data, we form a representation of reality, susceptible to being formalized in a concept that is able to express some necessary link among perceptions. At this point, through our reasoning, we give a meaning to our representation, reaching a plausible explanation of reality itself.

An essential first consideration must be made about the ways of perception. Pure perception does not exist: to see is a complex act of an essentially mental nature. Our perceptive experience is always linked to models, forms and general schemes. The pathologist, in daily practice, experiences that by looking through a microscope at the same specimen at later stages, he may happen to appraise different aspects of the same specimen at later stages, and capable of conditioning a different diagnosis.

There is deep link – as Licata states – between the mechanism of visual perception, the subjective experience in seeing and the processes through which our mind builds descriptions of the world (the observer’s memory, previous experiences, knowledge and aims). The role played by subjectivity is, then irreducible in the production of knowledge, and mistakes are the price to be paid for this creative activity of the brain in solving the complexities of reality.

As a result, one has to introduce a difference of value between second opinion – a second observer applies to the same specimen his/her own perception, educated through both different experience and knowledge in relation to the previous observer – and review, where the temporal evolution of the pathology conditions the completeness of the clinical information and, consequently, diagnostic interpretation, which under this circumstance, is applied to a case already largely solved.

However, the cognitive scheme referred to is susceptible to further implications for the pathologist.

If it is true that form, in nature, expresses function, it is also true, that, in histopathology, form is always perceived in relation to an artefact. Tissue vitality is, so to speak, interrupted and “captured” in a determined time. Later on, through the microscope, moving bi-dimensionally on a plane, one tries to identify the features of the object in its three-dimensionality and temporality. For the pathologist, the problem to tell between appearance and reality is compared with walking on a narrow ridgeway, where one has to continually seek a recomposition of the existing split between optic data (what is there) and epistemological data (our suppositions on what is there).

While, for the logic of knowledge, one plans to find out what is there, one may still attribute a certain validity to the thomistic notion of truth as adequatio intellectus et rei, that is as conformity between thought and reality, the logic of science is conjectural and inferential. In daily practice, the pathologist copes continually with notions of pragmatic truth, which imply the compliance with a rule (conventions), with consensus (guidelines, consensus conference, etc.), with usefulness and effectiveness (therapy).

Truth, more than a stable reference principle, becomes a regulatory ideal for the pathologist for his/her orientation, through successive approximations.

Truth exists, because reality by itself (pathology, illness), however difficult to determine, is not equivocal. Our interpretation may be equivocal and the “principle of sufficient reason” (nothing happens without a reason or that nothing occurs without it being possible to give an explanation about it) may come out to be, within our context, a two-edge weapon.

The problem will continue to be the correspondence between our perception, our representations and reality. In between, then, is language!

On our daily path the gap between true and likely, between certainty and truth, plays within the context of the distinction among univocal, equivocal or analogous concepts. It is a concept within which language takes on a prevailing value.

Ackermann, in Rome, as far back as 1982, started the first lesson of his seminar on dermopathology by stigmatizing the inaccuracies of language and terminology to be avoided in histopathology: “benign or malignant cells” (instead of the terms “typical” or “atypical”), “… which derives from …” (instead of “… which differ-
Robert Nozick has identified the following features of objectivity:

- independence of subjectivity (opinions, hopes, etc.);
- multiple access (one may have access to an objective fact from different perspectives and points of view);
- intersubjectivity (possibility for different subjects to find an agreement on an objective fact);
- invariance through transformations.

Let us see, then, which instruments are available to us for a correct interpretation (diagnosis) of what we observe.

We can then proceed to a simple recognition of a histopathological picture evident by itself. In this type of approach, more suitable to the ones who already have some experience, analogy can be useful. Analogy establishes a similitude due to an equality of relationship. Attention, however, must be paid! As the absence of a proof is not yet the proof of an absence, so likewise to establish a similarity does not mean to draw automatically an identity! To browse through an atlas at random to find an image which may overlap the picture observed on a histological specimen is one of the main sources of diagnostic error.

To recognize is not possible unless one already knows, even if one may know and be, at the same time, unable to recognize. It may happen in fact to look at a histological specimen, to consider all its details, to describe exactly its morphological features and, at the end, to classify the lesion in the wrong way.

Giovanni Morelli, educated as a physician, but fond of art and an accredited expert in attributing paternity to unsigned works, created an epistemological paradigm (Morelli’s Method) which attributed determining importance to the basic form that every great artist could paint in an absolutely personal way. As Di Napoli refers, knowing the basic principles of the language of forms, the detail is the indisputable indicator of authenticity. The fact remains that the whole is hardly ever equal to the sum of its parts – as the Gestalt theory has taught us – and in histopathology it is not possible to discriminate in a clear way between the validity of a small, magnification-only diagnostic approach (and consequently wider field of observation) and an approach aiming at the search of a detail able to justify the final diagnosis. Going further than the recognition of a histopathological picture, we implement – mostly unconsciously – logically interconnected reasoning structures, ranging from abduction, to reduction and to induction.

According to what Peirce stated, these three inferential procedures are a sequential process ordered in such a way that abduction proposes a hypothesis, an explanation in actual fact; deduction derives consequences from it; induction checks the extent to which consequences correspond with facts, i.e. it places the cases which show the initial hypothesis to be inadequate in evidence.

In other words, abduction is the process which, both through an act of intuition and through an inference, leads to explanations (narrowly speaking it is a form of reasoning in which the conclusion is accepted as it explains in an optimal way the available data. In other words, it leads to hypothesize the causes of known effects), whereas induction performs an essentially classifying function and regulates the empirical verification of the abducted hypotheses.

Among other things Peirce himself emphasizes that perceptive judgements must also be considered as “borderline cases of abduction”. Perceptions themselves are hy-
potheses, though unconscious, as the visual system does nothing but create a three dimensional perception of the world which is different from the bi-dimensional images projected on the retina. The fact that perception unifies the sensations of the perceived object in an unconscious way causes the same interpretation of the object to happen mostly in an uncontrolled manner and causes experience to do nothing but strengthen the nearly automatic application of our interpretative schemes.

In practice, having identified the problem, bearing in mind a suitable theoretical list of the nosological classes («enumerations will be so complete and reviews so general so as to be sure not to have left anything out»), as René Descartes advised), one proceeds to the attribution of the picture by evaluating the various diagnostic hypotheses which appear from time to time or by putting forward diagnostic hypotheses, inferring their consequences and verifying their coherence with clinical-instrumental data or through the application of ancillary methods.

We could state that a highly experienced pathologist will mainly trust the recognition of the histopathological picture; an induction-oriented pathologist will request many lab tests (immunohistochemistry, molecular biology tests, etc.) and, only with a number of data at his disposal, he/she will formulate a diagnostic hypothesis; a hypothetical-deduction oriented pathologist will aim at looking for only those signs which may explain a given pathology, requesting always specifically aimed ancillary tests.

Within the context of a hypothetical-deductive logic Bayes’s theorem may help. It allows, starting from the observed effects, calculating the verisimilitude of causes expressed in probabilistic terms. Bayes’s probabilities express the probability of an event in relation to conditions that have a certain probability. This allows us to review our choices depending on the information we acquire about their consequences (let us evaluate, by the way, the importance of acquiring complete clinical history information to give a correct diagnosis.)

Depending on the adopted diagnostic approach – in diagnostic histopathology – one may, then, write a clinical report with an analytical or (rather) descriptive, brief or categorizing or inductive character (… compatible with …).

As Federspil et al. stated, «… pathological anatomy is no longer only the domain of facts and observations, but it gives origin and includes within itself hypotheses, too» and then, «… while in traditional epistemology truth was an ideal that could be reached and error was a deviation from the right path leading to the knowledge of reality, for contemporary epistemology truth is only a regulatory ideal and the recognition of an error is an unavoidable stage in the progress of knowledge».

Where does a diagnostic error hide?

The literature often reports on histopathological peer reviews of selected particular case-studies, where important diagnostic discrepancies are regularly documented even among highly experienced pathologists.

Again, from literature data, it emerges that 40% of errors in diagnostic histopathology are due to difficulties of communication with the clinician. A larger number of mistakes occur because of the shortage of time available for diagnosis, poor familiarity with a method and inexperience.

Depending on the modes of the diagnostic approach, we have noticed that the categorization of a lesion or its experience-based, intuitive recognition, may produce a larger number of errors in comparison to the inductive method and the slower and analytical hypothetical-deductive method.

According to Coderre and colleagues, the recognition of the clinical picture is 10 times as efficient as the hypothetical-deductive method, but only for expert doctors. For students and beginners it is not recommended, as the consequences of possible errors may be extremely harmful. Induction through fields of knowledge is functional both for experts and beginners, and it may be five times more likely to yield diagnostic success compared to deductive-hypothetical reasoning.

Since, as Popper stated, only what we want to prove will occur, one must anyway avoid the implicit misunderstanding in the process of foreknowledge of the morphological picture, so that, therefore, if what I am unable to see does not correspond to what I expect to see, I will endeavour to regain it for my demonstration through the use of ad hoc criteria.

In this sense, particular attention must be paid to the so-called “coherent theories” of truth, according to which coherence of the explanation may be obtained by removing the evidence to the contrary through a selection of informative data.

The following are the most common causes of error that may occur during the cognitive process:

- incoherence between theories and facts (error of method);
- missing relationship between cause and effect;
- wrong interpretation of data from experience (perception, etc.);
- missing explicitness (failing in rendering explicit the conditions) of the conditions that make interpretation possible (the context, that is, in our case, the clinical history picture).

It may then be a question of errors in perception (an existing, but not unrecognized anomaly), interpretation errors and technical acquisition errors (sampling, etc.).

The difficulties of a complete representation of complex information are the bounds of the hermeneutical threshold of our cognitive approach.

Surely the world is not only one of our representations, but truth, – at least scientific truth – after all is always speculative.

Between reality and possibility, within our operative context, probability rather than necessity, is the most suitable criterion for truth. Truth ends up by being a task oriented towards a continuous unification and a rational justification of experience, rather than the identification of a presumed “reality in itself”.
Immunohistochemical investigations seem to deserve a separate consideration: their implementation has become imperative as an ordinary routine method. This is useful to establish a significant correlation between morphological and biological data through the identification of specific molecules, capable of revealing and defining the type of cellular function relating it to its histogenetic and structural features.

These methods meet, as it is known, important interpretation limits in poor specificity and/or in the aberrant expression of some markers, but above all in the interpretation of results, particularly if disjointed from morphological data.

In the light of the considerations made until now, it may be interesting to have a close examination of the categories of reasoning, which often guide us in the application of immunohistochemistry results, through the so-called “tables of truth”. These are tables used in formal logic to establish if a certain proposition is either true or false (values of truth of propositions).

If one observes through a microscope an undifferentiated tumour (meaning that morphological features do not allow to place it in a certain diagnostic class), one may request immunohistochemistry reactions to reveal their bio-receptorial features through which one may have a reliable diagnosis.

If one suspects, for example, that a tumour with epithelioid-type morphological features may be a carcinoma (CAR), one may request an immunohistochemical stain with pankeratin (CK). If this is positive, one will be able to state in general it is a carcinoma; if it is negative, one will say it is not a carcinoma.

What sort of reasoning is implied by these conclusions? We have two possibilities: a) we can say that “if the tumour is positive to cytokeratins, it will, then, be a carcinoma”, or b) we can say that “if the tumour is a carcinoma, it will, then, be positive to keratinas”.

The two instances of reasoning seem analogous. In actual fact, the reasoning (a) is not correct, as we know that other tumours may be positive to this antibody without being carcinomas (for example, an epithelioid sarcoma shows such behaviour). With (b) this reasoning we are not facing such interpretative obstacle. It will, however, be proved that the last type of reasoning – however, the only possible one – is wrong or, as we usually state in logic, is invalid.

For a further example, let us imagine that a pathologist observes a fusiform cell tumour and thinks, on the basis of its morphology, that it is a malignant schwannoma. He/she will request, as a confirmation, an immunohistochemical stain with the S-100 antibody – positive with neoplasias of this nature – and, if the stain is positive, he/she will opt definitely for the above-mentioned diagnosis. In reality, after successive investigations, if needed, and the application of additional ancillary methods (molecular biology, electronic microscopy, etc.) this neoplasia will turn out to be a synovial sarcoma.

The diagnosis was wrong, then, not only for the inconsistent interpretation between morphological and immunohistochemical data, but also because, as we will see, the basic reasoning was invalid.

Logic may be defined, generically, as the science of correct reasoning. Logicians have tried to formalize language, which is to translate it into formulas that they have applied the tables of truth to. Here, we will examine the ones pertaining to our discussion.

For enunciation, one means a sentence with a complete sense whose task is to be true or false. For instance, “Today it is snowing” is an enunciation, as in fact it may (true) or it may not (false) be snowing. Sentences which express orders, prayers, exclamations, etc. are not enunciations.

Symbols:
Brackets ( ) and [ ] are useful to underline enunciations linked by a connective.
The sign ∧ indicates the connective “and”.
The sign ¬ indicates negation.
The sign → indicates the conditional connective “if …… then”.
The sign ↔ indicates the double conditional connective “if, and only if …”.

Attention must be paid to not confuse the negation of an enunciation with its contrary. The negation of “white” is not “black”, but simply “non-white”.

The connectives useful for this discussion are examined. The negation of the enunciation A has the following table of truth:

<table>
<thead>
<tr>
<th>A</th>
<th>¬A</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>T</td>
</tr>
</tbody>
</table>

That is to say: the negation of a true enunciation is false, the negation of a false enunciation is true.

Even the conjunction “and” has its table of truth which establishes in an unequivocal way that the compound enunciation “A and B” (for instance, “The sky is blue and the sun is a star”) will be true only in the case that both enunciations A and B are true.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>A ∧ B</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>T</td>
<td>F</td>
<td>F</td>
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<td>F</td>
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<td>F</td>
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<td>F</td>
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</tbody>
</table>

If I say “It is winter and it is snowing”, and it is true that it is winter and it is snowing, in the last column of line 1 we will have T.
At line 2, if I say “It is winter and it is snowing”, whereas it is winter and it is raining (value F in the second

---

1 “Sensitivity” of a test = percentage of positive results in ill patients. “Specificity” of a test = percentage of negative results in subjects without a pathology.
column), then it will be obvious that the value of the last column will be F.
At line 3, if I say “It is winter and it is snowing”, whereas it is summer (value F in the first column) and it is snowing, for the same reason as in line 2 the value of the last column will be F.
In the end if I say (line 4) “It is winter and it is snowing”, whereas it is summer and it is raining, the value of the last column can but be F.
As far as our discussion is concerned, in reasoning we also have the so called “if … then” implication connective, as in the enunciation “If it snows tomorrow (A), then I will go to the mountains (B)”. The table of truth in this case will be:

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>A → B</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>T</td>
<td>F</td>
<td>F</td>
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<tr>
<td>F</td>
<td>T</td>
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<tr>
<td>F</td>
<td>F</td>
<td>T</td>
</tr>
</tbody>
</table>

To state that A implies B means that A is a sufficient condition for B, whereas B is a necessary condition for A, then A → B will be false only in the true A case and false B case.
If I say “If he is a pathologist then he is a physician”, we can see that in line 1 the result in the last column will be T. In fact, it is quite consistent to deduce one to be a physician from being a pathologist, as to be a pathologist it is necessary to hold a degree in medicine. Line 2 (F in the last column) says that if one is a pathologist one cannot but be a physician, again for the previous reason. Line 3 seems to be more counter-intuitive, because – even if on the left of the arrow – the value is false (F in the first column), in the last column one finds T, the reasoning will be correct. This is because the connective “→” implies only a state of sufficiency, i.e. it is sufficient to be pathologists to be physicians too, but it is not necessary to be so; in fact, I can be a surgeon (F in the first column) and, then, be a physician.
On the contrary, the inversion “←” implies the necessity to be a physician in order to be a pathologist, but it is not enough to deduce one to be a pathologist. In fact, one can be a surgeon or a radiologist or a paediatrician, etc.
Line 4 in the end expresses a counterfactual condition and says that if it is false to be a pathologist and it is false to be a physician, the reasoning will be valid anyway (T in the last column).
At this stage, starting on the assumption that all carcinomas are positive to CK, the reasoning, as in (b), will be: if it is a carcinoma, then it will be positive to cytokeratins … … and as keratins are positive, then it must be a carcinoma.
We can schematize the above-mentioned statement symbolically, too:

\[
\begin{align*}
\text{CAR} & \rightarrow \text{CK+} \\
\text{CAR} \quad \quad \text{-----------------------------------} \\
\text{CK+} \\
\end{align*}
\]

This form of reasoning (“if … then”) is called by logicians *modus ponens*: what in the ‘if-then’ proposition comes after will be true in fact if what precedes is accepted. This implication will be false if the premise is true and the conclusion is false. In the previous example (“If it snows tomorrow, then I will go to the mountains”), the enunciation will be false if it snows and I don’t go to the mountains.
From (1) the following possibility derives: the deduction is certainly right, but we cannot state the truthfulness of the fact that the tumour is a carcinoma (as we do not know about it *a priori*).
One more argumentation:

\[
\begin{align*}
\text{CAR} & \rightarrow \text{CK+} \quad \text{CK+} \\
\text{CAR} \quad \quad \text{-----------------------------------} \\
\text{CAR} \\
\end{align*}
\]

Here, the reasoning does not guarantee absolute certainty. It is defined “contingent” as we will see. In fact, the inversion of the reasoning does not offer the logical certainty of the result. CK+ is necessary, but not enough for CAR.
One more argumentation:

\[
\begin{align*}
\text{CAR} & \rightarrow \text{CK+} \quad \neg \text{CK+} \\
\text{CAR} \quad \quad \text{-----------------------------------} \\
\neg \text{CAR} \\
\end{align*}
\]

Here the reasoning is correct.

**Demonstration**

Let us analyze (1). It states “if CAR implies CK+, and if CAR is true, then also CK+ will be true”.

Formalizing:

<table>
<thead>
<tr>
<th>CAR</th>
<th>CK+</th>
<th>CAR → CK+</th>
<th>(CAR → CK+) ∧ CAR</th>
<th>[(CAR → CK+) ∧ CAR] → CAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
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</table>

* We exclude, in a theoretical way, the possibility for a carcinoma not to express CK and we suppose instead that all carcinomas express it.
The values one obtains in the last column are always T; in this case one says the reasoning is an instance of tautology. That is to say: the reasoning is always valid (if in the last column all the values were only F values, we would, then, have a contradiction: the reasoning would always be invalid). Of course, as it has already been said, the reasoning is of no use, as we cannot state with certainty that it is a carcinoma (as already said, we cannot be sure of the truthfulness of CAR).

Let us analyze (2). It states “if CAR implies CK+, and if CK+ is true, then also CAR will be true” (similarly to reasoning b). Formalizing:

<table>
<thead>
<tr>
<th>CAR</th>
<th>CK+</th>
<th>CAR → CK+</th>
<th>(CAR → CK+) ∧ CK+</th>
<th>[(CAR → CK+) ∧ CK+] → CAR</th>
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<td>T</td>
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The values in the last column are both T and F: one says that the reasoning is contingent. That is: the reasoning may be correct, but the conclusion may be true by chance.

Let us analyze (3). If I say “CAR → CK+” then I can say that “if CAR implies CK+, and if CK+ is not true, then also CAR will not be true”.

Formalizing:

<table>
<thead>
<tr>
<th>CAR</th>
<th>CK+</th>
<th>¬ CAR</th>
<th>¬ CK+</th>
<th>CAR → CK+</th>
<th>(CAR → CK+) ∧ CK+</th>
<th>[(CAR → CK+) ∧ CK+] → CAR</th>
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</thead>
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<td>T</td>
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</tbody>
</table>

Here, too, the values obtained in the last column are always T, therefore the reasoning is an instance of tautology, then valid. If keratin is negative, it is always logically true that it is not a carcinoma.

There are also immunohistochemical reactions to which one cannot apply the connective “if … then”, but the connective “if, and only if …” (biconditional), in which the antecedent of one is the consequent of the other and vice versa (for example: “if and only if it is a triangle, then it will have three sides and if and only if it has three sides, then it will be a triangle”). A typical immunohistochemical reaction to which the biconditional must be applied is the determination of the prostate base (basal) cells through 34βE12.

The table of truth of the biconditional is:

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>A ↔ B</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>T</td>
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</table>

A ↔ B is true if and only if A and B are both true or are both false.

In the connective “A → B” one says that A implies B, whereas in the connecting “A ↔ B” one says that A bi-implies B. To use the example “If it rains tomorrow, then I will go by car”, I can say “If, and only if, it rains tomorrow, then I will go by car”. The first case is equivalent to saying “Tomorrow I will go by car if it rains”. The second case is equivalent to saying “Tomorrow I will go by car only if it rains” (in this case going by car is subordinate exclusively to the fact that it rains and, then, if it does not rain, I will not go by car).

Formalizing the biconditional we can say that “if, and only if, A implies B, then A implies B and B implies A”.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>A ↔ B</th>
<th>A → B</th>
<th>B → A</th>
<th>(A → B) ∧ (B → A)</th>
<th>(A ↔ B) → [(A → B) ∧ (B → A)]</th>
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<tbody>
<tr>
<td>T</td>
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</table>
The data of the last column are all T and, then the reasoning is valid and in fact, unlike (2), the B → A inversion is allowed.

Having established that (2) is not a valid instance of reasoning, some considerations will follow:

• as we cannot entrust a scientific result to invalid reasoning, every immunohistochemical investigation must be conducted, when possible, using the highest number of antibodies to ensure the chances of a correct result;
• in very complex cases, where morphology is not a reliable reference, an immunophenotypical diagnosis can but be compatibility;
• is the only valid reasoning, that is to say that only a negative reaction offers the “logical certainty” of the diagnostic attribution;
• proposals for new pathological entities (“new entities”) – identified only in relation to immunohistochemical evidence – require particular care before proposal.

The above-mentioned formalizations are not, obviously, exhaustive. They are part of the logic necessary for the formalization of scientific language. Logic, at any rate, does not replace the knowledge of surgical pathology, but above all, logic opens up a possibility to formulate new explicative hypotheses (abduction). (It is known that negativity to an immunohistochemical reaction for S-100 strengthens, instead of contradicting, a diagnosis of a suspect melanoma of the nasal cavities or that negativity to reaction for 34βE12 keratin does not necessarily indicate the absence of basal cells, even in fully normal prostate glands).

On the other hand, though experience offers only probabilistic approximations to certainty and formal logic represents a style of thought which is different from reasoning through hypotheses, one cannot leave aside the need for every explanation to be presented as a logical derivation.

In this view, the value of the same immunohistochemical investigations, in diagnostic histopathology, at the close examination of the assumptions of formal logic, does not seem to be able to play the role of support and diagnostic completion by comparison with morphological data.

In conclusion regarding the mentioned problems, pertaining to the complexity implied in diagnostic histopathology, it seems proper and fit to conclude with the same considerations made by Zampieri about models and theories in the history of pathological anatomy: «The past proves we cannot say true things about the world – true to the extent which allows us to get better results by comparison with previous endeavours – even starting from models of reality which are just rough or partly incorrect. This means that to create good science there seems to be something even more important than the model we use to interpret phenomena, and that is the way we use it.»

References

Histological evaluation of papillary lesions of the breast from needle biopsy to the excised specimen: a single institutional experience

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St. John Hospital and Medical Center, Detroit, Michigan

Key words
Breast cancer • Biopsy • Papilloma • Papillary neoplasms • Differential diagnosis • Surgery

Summary

Background. The assessment and categorization of papillary lesions remains one of the most challenging areas in breast pathology. We evaluated the histological follow-up of papillary lesions of the breast from needle core biopsy to final excision to determine whether these lesions warrant excision, irrespective of histologic subtype.

Study Design. A total of 91 needle core biopsies from the breast diagnosed as “papillary lesions” at our institution from January 2001 to June 2011 were included in the study. Twenty-nine of these (mean patient age 54.93 ± 12.5 SD) were reported as benign papillary lesions, and the remaining 62 (mean patient age 61.98 ± 15.20 SD) were diagnosed as either atypical papillary lesions (17 cases) or malignant papillary lesions (45 cases).

Results. Of the 29 needle core biopsies reported as benign, 19 cases (65.5%) were diagnosed as benign and three (10.3%) were diagnosed as malignant on follow-up. The remaining seven cases did not proceed to excision. Sixty-two of the 91 cases were given a diagnosis of either atypical papillary lesion or malignant papillary lesion on needle core biopsy. Of the 45 cases initially diagnosed as malignant, 44 (97.7%) were eventually deemed malignant and one atypical ductal hyperplasia (ADH) was found upon excision. The initial diagnosis of atypical papillary lesion was rendered in 17 cases, of which 10 turned out to be malignant, five ADH, and two benign on excision.

Conclusion. We conclude that if a benign papillary lesion is present on initial needle core biopsy, then the probability of malignancy is high (10.3%) on the final excision. Similarly, all malignant papillary lesions diagnosed on needle core biopsy should be excised due to the very high likelihood (97.7%) of a diagnosis of malignancy on final excision. Based on our results, we suggest surgical excision of any papillary lesion diagnosed on needle core biopsy.

Introduction

The diagnosis of the papillary lesions of the breast on the core biopsies is very challenging. Papillary lesions of the breast are commonly encountered in routine surgical pathology and comprise a heterogeneous group that includes papilloma, atypical papilloma, non-invasive papillary carcinoma, and invasive papillary carcinoma. Papillary lesions may create diagnostic difficulties because papillae are encountered in both benign and malignant processes. Needle core biopsies aid in the initial diagnosis of breast lesions, but the presence of papillary structures is a cause for concern and careful follow-up is recommended. Comparing the initial diagnosis provided on needle core biopsy with the final diagnosis rendered on excisional biopsy is essential in confirming whether a malignant papillary lesion diagnosed on needle core biopsy is truly malignant. The single most valuable histologic feature that distinguishes malignant from benign papillary breast lesions is the presence of an atypical epithelial proliferation of a single cell type. Thorough sampling of papillary lesions is a major concern in correctly classifying papillary lesions at needle core biopsies; therefore, the treatment of papillary lesions diagnosed at needle core biopsy remains controversial. Some authors advocate observation of papillary lesions when the needle core biopsy is considered benign, while others recommend surgical excision of all papillary lesions regardless of histologic subtype. We analyzed our institutional experience with papillary lesions of the breast in order to further investigate the correlation between initial and final diagnoses of these entities.
Materials and methods

Prior to its initiation, this study was reviewed and approved by the Institutional Review Board Committee (IRB) at the parent institution, St. John Hospital and Medical Center in Detroit, Michigan (USA). We retrospectively reviewed our laboratory information system database for all cases of adult female patients diagnosed on needle core biopsy with papillary lesions of the breast between January 2001 and June 2011. A comprehensive search of needle core biopsies of the breast with any combination of the words “papillary”, “breast”, and “lesion” in the main diagnostic line returned 98 results. Of these, 91 archival routinely-processed, formalin-fixed, paraffin-embedded surgical pathology specimen cases with follow-up resection specimens available for histologic evaluation were retrieved; they included all histologic subtypes of papillary lesions of the breast. Twenty-nine of these (mean patient age 54.93 ± 12.5 SD) were reported as benign papillary lesions (Fig. 1), and the remaining 62 (mean patient age 61.98 ± 15.20 SD) were diagnosed as either atypical papillary lesions (17 cases) or malignant papillary lesions (45 cases) (Figs. 2, 3, 4). The remaining seven cases were diagnosed either as atypical papillary lesion or frankly malignant on needle core biopsy, and follow-up specimens were unavailable. These seven cases were not included in our study.

The 29 benign lesions were not associated with any atypical features, carcinoma in-situ, or invasive carcinoma. The 17 atypical lesions generally exhibited a greater extent of epithelial proliferation with florid hyperplasia and atypical architectural patterns, but the degree of atypia did not meet the diagnostic threshold for in-situ or invasive carcinoma. The presence and specific location of associated atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) was documented. The 45 malignant lesions diagnosed as in-situ or invasive carcinoma demonstrated irrefutable features of malignancy.

Results

Of the 29 needle core biopsies reported as benign, 19 cases (65.5%) were diagnosed as benign and three (10.3%) were diagnosed as malignant on follow-up (Table I). The remaining seven cases did not proceed to excision. The three malignant cases included two cases of ductal carcinoma in-situ with micropapillary features and one lobular carcinoma in-situ (Table II).
Sixty-two of the 91 cases (68.1%) were given a diagnosis of either atypical papillary lesion or malignant papillary lesion on needle core biopsy. Forty-five cases were diagnosed as malignant on the initial biopsy specimen, with 44 (97.7%) of the cases determined to be malignant and one of the cases atypical ductal hyperplasia (ADH) on follow-up (Table III). A diagnosis of atypical papillary lesion was rendered in 17 cases, 10 of which turned out to be malignant, five ADH, and two benign on final excision (Table IV).

We compared all 62 of cases with a final diagnosis of either atypical or malignant papillary lesion on initial needle core biopsy, excluding the cases with benign diagnoses, to the final excisional biopsy findings. Of these 62 cases, only two cases (3.2%) were diagnosed as benign on final excision. Overall, of the 91 total cases included in our study, 21 (23.1%) were found to be benign and 62 cases (68.1%) were determined to be atypical or malignant on final microscopic examination.

**Discussion**

Papillary proliferations of breast form a spectrum of lesions ranging from intraductal papilloma to in-situ or...
invasive carcinoma. These lesions are often difficult to evaluate fully by needle core biopsy because these specimens are usually not representative of the entire lesion. Intraductal papillary lesions are frequently heterogeneous, and the chance of missing the malignant component on biopsy specimens is significant. Indeed, the probability of discovering atypia or malignancy within, or in close proximity to, the index lesion on review of the complete excision specimen is high. Some authors suggest that not all papillary lesions require surgical excision, whereas others have recommended complete removal of all type of papillary lesions diagnosed on needle core biopsy based on their complexity.

Based on our study, we found that papillary lesions of the breast with an initial benign diagnosis on needle core biopsy may still turn out to be malignant on the follow-up excision specimens. Three of the cases included in our study were originally diagnosed as benign on needle core biopsy but later proved to be malignant on excision (Fig. 5). Oftentimes, these lesions harbour a malignant component that may not be sampled adequately by needle core biopsy, and the specimen may not be representative of the entire lesion. On the contrary, virtually all (97.7%) of the papillary lesions initially diagnosed as malignant on needle core biopsy were confirmed to be malignant on review of the final excision (Table III).

There is no question that needle core biopsy is an essential tool for the initial diagnosis of breast lesions and planning of further management. However, needle core biopsy is not without disadvantages. There is a chance that a core biopsy specimen may not be representative of the actual lesion due to sample size limitations. In addition, performing needle core biopsies may result in the displacement of epithelium into the surrounding tissue and lymphovascular channels. While this may not cause much of a problem when the papilloma is not involved by atypia, the potential for misinterpretation is much greater if the entrapped epithelium is dislodged from an area of carcinoma, whether in-situ or invasive, within a papilloma or an encapsulated papillary carcinoma. The presence of myoepithelial cells plays an important role in classifying the papillary lesion, especially in differentiating a papilloma from a papillary carcinoma. The most reliable immunohistochemical marker for staining myoepithelial cells is nuclear staining by p63.

Based on our study results, the likelihood of diagnosing a malignant papillary lesion of the breast on the final excision is greater than 10% despite an initial benign diagnosis. We recommend that all papillary lesions diagnosed on needle core biopsy, regardless of their cytological and architectural features, are completely excised.

**Conclusion**

Based on our study results, the likelihood of diagnosing a malignant papillary lesion of the breast on the final excision is greater than 10% despite an initial benign diagnosis. We recommend that all papillary lesions diagnosed on needle core biopsy, regardless of their cytological and architectural features, are completely excised.

**Conflicts of Interest**

None.

References


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Introduction

Ectopic pancreas is defined as pancreatic tissue outside the normal location without connection to the normal pancreas. The frequency is relatively uncommon, seen in less than 0.5% of laparotomies carried out for upper abdominal conditions and in 0.6-13% of autopsies. Most cases are asymptomatic and are identified as incidental findings. It occurs in both abdominal and extra-abdominal locations, most commonly in the stomach (25-60%), followed by the duodenum (25-35%) and jejunum (16%). It may develop the same pathological changes of a normal pancreas such as acute pancreatitis and cyst formation. Malignant degeneration rarely occurs. We present a case of heterotopic pancreatic adenocarcinoma localized in the duodenal bulb presenting with symptoms of gastric obstruction.

Case report

An 86-year old woman was admitted to the Surgery Department with abdominal pain localized at upper quadrants, nausea and vomiting. The patient reported a two-month history of abdominal pain and dyspepsia, in particular after meals. On physical examination, the right upper abdomen was tender with a positive Murphy’s sign and negative Blumberg’s sign. A double contrast barium meal of the upper gastrointestinal tract demonstrated gastrectasia and abdominal ultrasound revealed a single stone (diameter 8 mm) located in the gallbladder. A diagnosis of acute cholecystitis was performed and the patient was operated on with laparoscopic approach. During the surgical procedure pyloric stenosis with gastrectasia was observed, and an intraoperative endoscopy suggested the presence of a neoplastic stenosis. A sub-total gastrectomy with duodenal bulb resection, a complete lymph node D2 dissection and cholecystectomy were performed with an open surgical approach and the intestinal transit was restored with a gastro-jejunal antecolic and antiperistaltic anastomosis (Billroth II). Gross examination revealed an infiltrating and stenosing tumour, 3 cm maximum diameter, located in the pylorus-duodenal bulb. On sectioning, the tumour showed an intramural growth pattern, thickening...
and stenosing the wall. On microscopic examination, it consisted of neoplastic glands dispersed into a desmoplastic stroma invading the entire thickness of the wall and extending into the periparietal soft tissue. The degree of differentiation varied from well-formed glands with mucinous cytoplasm and minimal cytologic atypia to poorly formed glands and cells with marked cytologic atypia infiltrating singly or forming solid sheets. Normal pancreatic tissue with acini, ducts and islet cells was present within and near the adenocarcinoma (Fig. 1). Some of these ducts showed pancreatic intraepithelial neoplasia, PanIN-2, with uniform columnar cells and basally located uniform nuclei and papillary architecture (Fig. 2). The patient was discharged 10 days after the operation without any complications. At present, the patient is in a good clinical condition. The last CT scan (September 2012) showed multiple hepatic metastases. Chemotherapy was not performed due to the advanced age of the patient.

**Discussion**

Ectopic pancreas is often asymptomatic; it may become clinically evident when complicated by pathologic changes such as inflammation, bleeding, obstruction and malignant transformation. Malignant transformation is rare and about 30 well-documented cases in literature have been described \(^4\)\(^{10}\). In a review of the literature, Emerson et al. \(^4\) reported that the majority of well-documented cases occurred in the stomach (56%), with the jejunum and duodenum representing the next most frequent sites of occurrence at 15% and 11% of cases, respectively. According to Guillou et al. \(^1\), the malignant transformation of ectopic pancreas may be diagnosed only if three conditions are present: 1) the tumour must be located within or close to the aberrant pancreatic tissue; 2) transition between pancreatic structures and the carcinoma must be observed; 3) ectopic pancreatic tissue must contain at least fully developed acini and ducts. In our case, these criteria were fulfilled as well as the absence of a primary neoplasm of the pancreas and evidence of ectopic pancreas in the duodenal wall. The majority of carcinomas arising within the reported examples of ectopic pancreas have been adenocarcinomas showing ductal differentiation. The progression model of ductal adenocarcinoma from pancreatic intraepithelial neoplasia (PanIN) is also applicable to the ectopic pancreas \(^11\). In our case, the presence of intraepithelial neoplasia (PanIN-2) adjacent to the invasive adenocarcinoma supports this observation. Preoperative diagnosis of ectopic pancreas is often difficult with conventional imaging studies. CT and ultrasonography are not specific, showing the presence of a mass; upper endoscopy often fails because the ectopic pancreatic tissue is localized deep in the duodenal mucosa or in submucosal layer \(^12\)\(^{13}\). The prognosis of an adenocarcinoma arising in an ectopic pancreas is not known because of the small number of reported cases. Survival seems better than that of primary pancreatic carcinoma \(^2\), probably for the earlier clinical presentation of the carcinoma in ectopic pancreas \(^14\). However, the overall prognosis remains poor with 5-year survival rates of 10-27% following resection \(^15\).

**Conflicts of Interest**

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References


Pulse granuloma involving Meckel’s diverticulum: a case report and literature review

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Key words
Meckel’s diverticulum • Pulse granuloma

Summary
Pulse granuloma is a rare, benign entity that most likely represents a reaction to vegetable material and is characterized by hyaline rings and foreign-body giant cells. We report a case of a pulse granuloma involving Meckel’s diverticulum. The patient presented with abdominal pain and radiological findings consistent with Meckel’s diverticulum. Microscopic examination of the resected tissue confirmed diagnosis of Meckel’s diverticulum with small bowel mucosa. Peridiverticular foreign-body giant cells, hyaline rings and circular structures containing calcified basophilic granules were also identified, consistent with pulse granuloma. Pulse granulomas have been reported in a variety of locations, most commonly in the oral cavity. To the best of our knowledge, this is the first reported example of pulse granuloma in Meckel’s diverticulum. Familiarity with pulse granuloma allows for the timely and accurate diagnosis of this entity, particularly in sites not previously described in the literature.

Introduction
Pulse granuloma is a rare, benign entity, commonly thought to be an inflammatory response to vegetable material and characterized by hyaline rings and multinucleated giant cells. Pulse granulomas have been most frequently reported in the oral cavity, but they have also been reported in the lungs following aspiration, the colorectum in association with diverticula, the rectum, the periprostatic soft tissue, the urinary bladder associated with interstitial cystitis and in intestinal fistulae involving the gallbladder, fallopian tube and skin. To the best of our knowledge, we report the first case of a pulse granuloma involving Meckel’s diverticulum.

Case Report
A 60-year-old Caucasian man presented with acute right lower quadrant abdominal pain. Abdominal computed tomographic scan showed a 2.4 x 2.2 cm collection of extraluminal fluid in close proximity to the distal ileum, with perforated Meckel’s diverticulum included in the differential diagnosis. The patient was admitted, treated conservatively with antibiotics, and discharged with surgical follow-up.

Two weeks after presentation, radionuclide imaging performed with 10 mCi of intravenous pertechnetate showed no focal areas of radiotracer uptake. Six weeks after presentation, repeat abdominal computed tomographic scanning showed improved inflammation with a corresponding tubular, fluid-filled, blind-ended pouch communicating with the distal ileum, consistent with Meckel’s diverticulum. An upper gastrointestinal series with small bowel follow-through also supported a diagnosis of Meckel’s diverticulum. The patient continued to report right periumbilical discomfort and diagnostic laparoscopy with resection was performed three months after initial presentation. Per the operative note, the diverticulum was identified in the ileum, approximately two feet from the ileocecal valve.

Grossly, the resected specimen consisted of a tan-pink pouch of soft tissue measuring 2.2 x 1.7 x 0.7 cm with a stapled surgical margin. Opening the specimen revealed unremarkable tan-pink mucosa with adherent yellow-tan...
material. The specimen was submitted in its entirety for permanent sections.

Review of sections showed a diverticular structure with small bowel mucosa with a peridiverticular, mono- and multinucleated histiocytic granulomatous inflammatory reaction, consistent with foreign-body giant cells (Fig. 1). Also identified were hyaline rings and circular structures containing calcified basophilic granules (Fig. 2), confirmed by von Kossa stain. No gastric mucosa was identified. A Congo red stain was negative for amyloid deposition. Grocott’s methenamine silver (GMS), periodic acid schiff (PAS), Ziehl-Neelsen stains were negative for fungal organisms and mycobacteria, respectively. Parasitic organisms were not identified. Polariscopy failed to detect vegetable material.

Discussion

Pulse granuloma is a rare, benign inflammatory lesion thought to be a response to foreign vegetable material. “Pulse” refers to “the edible seeds of various crops (as peas, beans, or lentils) of the legume family” rather than the regular, palpable arterial expansion more familiar to physicians. Pulse granuloma, however, is one of many names for this entity, reflecting some controversy over its pathogenesis. Other designations include: hyaline ring granuloma, chronic periostitis, granuloma in edentulous jaws, giant cell hyaline angiopathy, food-induced granuloma and oral-vegetable granuloma.

The exogenous theory of pathogenesis of pulse granulomas is currently favoured and suggests that the hyaline rings found in these entities are secondary to vegetable material penetrating the mucosa in question. In fact, experimental production of these entities in animals and the accumulation of additional cases support this theory. By contrast, the less favoured endogenous theory of pathogenesis suggests that the hyaline rings are due to hyaline degenerative changes in blood vessel walls. Oral pulse granulomas have been described in the literature since the late 1950s, with at least 173 cases documented. Similarly, extra oral pulse granulomas have also been reported since the mid-20th century, although much less frequently. Remarkably, the first case involving the gastrointestinal tract was reported in 2001 in a rectal mass. The pulse granuloma described above is only one of a few involving the gastrointestinal tract and the first involving Meckel’s diverticulum.

Described in 1809 by the German anatomist, Johann Friedrich Meckel, Meckel’s diverticulum is the most common congenital abnormality of the gastrointestinal tract, present in 1% to 3% of the general population. Meckel’s diverticulum arises from the proximal portion of the vitelline or omphalomesenteric duct, which normally persists beyond the early weeks of embryogenesis. As in this case, the resulting diverticulum typically communicates with the ileum, within one meter of the ileocecal valve.

Meckel’s diverticulum is of no clinical significance, until symptomatic complications of the structure arise. The most common complication of Meckel’s diverticulum is gastrointestinal haemorrhage, representing 25% to 50% of complications. Haemorrhage is typically caused by ulceration secondary to heterotopic gastric oxyntic mucosa, which was not identified in this case. Other complications include obstruction (25%) and, consistent with this case, diverticulitis (20%). Complications are most common in the paediatric population. However, this case is an excellent reminder that Meckel’s diverticulum and its associated complications should be considered in adults as well.

Approximately half of Meckel’s diverticula contain heterotopic epithelium. As mentioned above, the most common heterotopic epithelium found in Meckel’s diverticulum is gastric oxyntic mucosa. Gastric mucosa was not identified in this case, neither on radionuclide imaging nor on microscopy. Radionuclide imaging of Meckel’s diverticulum is performed with pertechnetate, an anion taken up by gastric mucosa, both homo- and heterotopic. False negative results have been reported due to small amounts of gastric mucosa, rapid washout of pertechnetate or impaired blood supply to the Meckel’s diverticulum. In this case, the pulse granuloma described above is only one of a few involving the gastrointestinal tract and the first involving Meckel’s diverticulum.

![Fig. 1. Low magnification of the Meckel’s diverticulum with small bowel mucosa and adjacent area of granulomatous inflammation with hyaline rings and circular structures containing calcified basophilic granules (haematoxylin-eosin, original magnification x100).](image1)

![Fig. 2. High-power view demonstrating foreign body giant cells, hyaline rings, and circular structures containing calcified basophilic granules (haematoxylin-eosin, original magnification x400).](image2)
Pulse granuloma involving Meckel’s diverticulum

The differential diagnosis in this case included infectious agents and vascular processes. Special stains described above were negative for fungal organisms and mycobacteria. The circular structures containing calcified basophilic granules were initially concerning for a parasitic infection, but closer examination excluded this. Additionally, while the described hyaline rings resemble vascular structures, the expected structures of blood vessel walls were entirely absent. A vascular process was therefore excluded. Also excluded was the possibility that the hyaline rings were the result amyloid deposition. A Congo red stain was negative for amyloid deposition. While pulse granulomas are a rare finding, familiarity with this entity allows for its timely and accurate diagnosis. Awareness of this entity likely facilitates its identification in other unique locations and may further support the purported theory of pathogenesis.

References

Sclerosing stromal tumour of the ovary: two case reports

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Key words
Sclerosing stromal tumour • Ovary • Sex cord-stromal tumours

Summary
Sclerosing stromal tumours are rare benign ovarian neoplasms of the sex cord stromal that occur predominantly in the second and third decades of life. Herein, we report two cases of sclerosing stromal tumour of the ovary. The two patients were 16 and 45 years old and both presented with pelvic pain. Ultrasonography demonstrated a heterogeneous solid mass of the left and right ovary, respectively, with some cystic foci in the second ovary. Laboratory tests including tumour markers and serum hormonal assays were normal in both cases. The two patients underwent left and right salpingo-oophorectomy, respectively. Microscopically, the tumours showed a pseudolobular pattern with cellular areas separated by oedematous and collagenous areas. The cellular areas were richly vascularized, with a hemangiopericytic pattern, and were composed of an admixture of theca-like and spindle-shaped cells. Immunohistochemical studies showed that the tumour cells were positive for smooth muscle actin, inhibin and vimentin, but negative for cytokeratin. The final pathological diagnosis was sclerosing stromal tumour. Postoperative course was uneventful for both patients.

Introduction
Sclerosing stromal tumour (STT) is an uncommon subtype of ovarian stromal neoplasms of the sex cord stromal with distinctive clinical, pathologic and radiological features that differentiate it from other stromal tumours. Since its initial characterization by Chalvardjian and Scully in 19731, there have been fewer than 100 case reports of this rare neoplasm.2 Herein, we report two cases of SST in a young girl and in a postmenopausal woman. Our aim was to highlight the clinicopathological features of this rare tumour with special emphasis on differential diagnosis.

Clinical history
Case 1. A 16-year-old female with no significant past medical history presented with complaints of pelvic pain and menstrual irregularity lasting three years. Pelvic examination revealed a tumour mass in the left iliac fossa. Ultrasonography demonstrated a well-delineated heterogeneous predominantly solid mass of the left ovary (Fig. 1). The right ovary was normal. All tumour markers and serum hormonal levels were within normal range. The mass was diagnosed as benign by frozen section analysis and removed by salpingo-oophorectomy. The surgical specimen was an oval, sharply demarcated mass with a smooth and intact outer surface measuring 15 x 11 x 7 cm. The cut surface revealed solid, cystic and oedematous areas. No haemorrhage or necrosis was

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observed. Histologically, the tumour was composed of ill-defined cellular pseudolobules separated by a densely hyalinized stroma. (Fig. 2) The lobules were composed of a population of two-cells: rounded polyhedral cells with eosinophilic or vacuolated cytoplasm, and spindle shaped fibroblasts (Fig. 3). Mitotic figures were absent. Cellular areas revealed a rich thin-walled vascular network. Periodic acid-Schiff and mucicarmine stains were negative. Immunohistochemical analysis demonstrated positivity for inhibin, vimentin and smooth muscle actin (Fig. 4) and negativity for cytokeratin. At the periphery of the mass, residual ovarian tissue was identified. The final pathological diagnosis was SST of the ovary. Post-operative recovery was uneventful. The patient has been followed on an outpatient basis without specific findings.

Case 2. A 45-year-old nulliparous previously healthy woman presented with pelvic pain of 11 years’ duration. She attained menopause at the age of 34 and had regular menstrual periods. On clinical examination, there was no palpable mass. Ultrasonography showed a heterogeneous predominantly solid mass of the right ovary measuring 3.7 cm in diameter with some cystic foci (Fig. 5). The contralateral ovary was normal. For further evaluation of the lesion and adnexa, magnetic resonance imaging (MRI) was carried out and revealed a well-circumscribed solid mass that was heterogeneous and low in signal intensity, but contained extremely low-signal-intensity components posteriorly. All laboratory tests including tumour markers and serum hormonal assays were normal. The mass was considered benign by frozen section analysis. The patient underwent right salpingo-oophorectomy. On gross examination, the right ovary was enlarged, measuring 4.5 x 3.2 x 2 cm, weighing 19 g. On cut section, it was almost entirely replaced by a greyish-white, firm, rubbery tumour with a focal gelatinous and cystic appearance. Microscopically, the tumour showed a pseudolobular pattern with cellular areas separated by oedematous and collagenous

![Fig. 2.](image1.png)

The tumour shows a pseudolobular pattern consisting of cellular and hypocellular hyalinized areas with a conspicuous hemangiopericytoma-like vascular pattern. (haematoxylin & eosin, original magnification x 10).

![Fig. 3.](image2.png)

The cellular area is composed of vacuolated cells and spindled fibroblast-like cells with a haemangiopericytoma-like vascular pattern (haematoxylin & eosin, original magnification x 40).

![Fig. 4.](image3.png)

Tumour cells are positive for smooth muscle actin. (immunohistochemistry, original magnification x 40).

![Fig. 5.](image4.png)

Case 2: Abdominal ultrasonography showing a heterogeneous predominantly solid mass of the right ovary with some cystic foci.
areas. The cellular areas were richly vascularized, with a haemangiopericytic pattern, and were composed of an admixture of theca-like and spindle-shaped cells. Immunohistochemical study showed that tumour cells showed diffuse immunostaining for actin, inhibin and vimentin, but were negative for cytokeratin. Postoperative course was uneventful. At present, the patient is in follow-up.

**Discussion**

Sclerosing stromal tumour is a rare benign neoplasm that accounts for 2-6% of all ovarian stromal \(^3\). More than 80% of SST occur below 30 years of age \(^4\). Our two patients were 16 and 45 years old. Common presenting clinical symptoms are pelvic pain, hypermenorrhoea and menstrual irregularities. Although these tumours were initially believed to be non-functional \(^1\), \(^5\), there have been more recent reports suggesting the presence of hormone production both from a biochemical standpoint and associated manifestations of infertility and irregular menses \(^6\). Hormonal effects such as masculinization are uncommon \(^7\). Ultrasonography is a useful initial tool for differentiating between cystic and solid masses and determining the organ of origin \(^8\). However, computed tomography and MRI are both more sensitive for delineating the nature of the mass and tumour extension. On MRI, a diagnosis of SST can be strongly suggested, when typical signal patterns such as hypointense nodules, hyperintense stroma, lobulation, strong enhancement with gadolinium and a peripheral hypointense rim are present \(^8\). Due to the rarity of this particular ovarian neoplasia, it is not always possible to predict the presence of this tumour preoperatively on the basis of clinical and sonographic findings. All SST of the ovary reported in the literature were benign and were treated successfully by enucleation or unilateral anexectomy. Macroscopically, the tumour is typically unilateral and sharply demarcated, measuring 3-17 cm in diameter. The sectioned surface is solid, grey-white with occasional yellow foci and usually contains oedematous or oedematous stroma. The cellular areas separated by hypocellular areas of densely collagenous or oedematous tissue. The cellular areas contain prominent thin-walled vessels with varying degrees of sclerosis admixed with both spindle and round cells, the latter may resemble luteinized theca cells or show perinuclear vacuolization \(^3\). Immunohistochemically, the cells of SST are positive for vimentin, smooth muscle actin, \(\alpha\)-inhibin and CD99; they are negative for S-100 protein and epithelial markers \(^6\). Depending upon which component is most prominent in the tumour, the entities to be considered in the differential diagnosis can vary. If the spindle cells predominate, a SST may be confused with a fibroma or luteinized thecoma. Fibroma tends to occur in older patients, which upon histology frequently show hyalinized plaques and lack the pseudolobulation, prominent vascularity and cellular heterogeneity characteristic of SSTs. Luteinized thecoma and SST show several clinical and pathologic features. Both occur in young patients more frequently than fibromas or thecomas. Both are stromal tumours containing spindled and lutein cells, and express inhibin and calcitriol. However, the variegated appearance of SST and its prominent thin-walled vessels are absent in luteinized thecoma. Because the lutein cells of SST often have clear cytoplasm, and sometimes a signet-ring cell appearance, they can mimic metastatic signet-ring cell carcinoma. Krukenberg tumours, however, contain mucin and are positive for keratin and EMA, while the vacuoles in the signet-ring-like cells of the SST contain lipid. The aetiology of SSTs is unknown \(^10\). SSTs are proposed to derive from a population of muscle-specific actin-positive elements from the theca externa, namely perifollicular myoid stromal cells. The vascular, sclerotic and oedematous stromal changes are constant features of these tumours and relate to the local elaboration of some vascular permeability and growth factors like VPV and VEGF \(^10\). On the other hand, some authors have suggested that endocrine milieu might be responsible for the morphology of SST and may develop from pre-existing ovarian fibromas.

In summary, two cases of ovarian SST are reported along with radiological and pathological findings. It is difficult to distinguish SSTs consisting of solid and cystic areas from ovarian malignancies on the basis of radiological and macroscopic examination, as these tumours additionally appear very vascular giving the impression of malignant tumours. A definite diagnosis of SST is established only by histological examination, but at diagnosis of benign ovarian tumour is possible intraoperatively via frozen section analysis by examining the background of pseudolobular pattern, heterogeneity of the cellular areas and densely hyalinized or markedly oedematous stroma.

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Introduction

Cardiac myxoma is the most common benign cardiac tumour accounting for 25% of all heart tumours and 50% of benign ones\(^1\). Because of the lack of specific clinical signs, its diagnosis can be challenging. Asymptomatic course with incidental diagnosis is relatively frequent. These tumours must be treated surgically as soon as possible, but care must be taken to avoid possible pitfalls.

Materials and methods

We reviewed 6 cases of patients with cardiac myxoma managed in the Departments of Cardio-Thoracic Surgery and Pathology. Cases were diagnosed over a 12-year-period, from 2000 to 2012. Information on age, sex, presenting symptoms, ultra-sound characteristics, surgical procedures and follow-up were obtained from patient medical records. In all cases, trans-thoracic ultra-sound examination was performed as an essential diagnostic tool in addition to chest X-ray and ECG. CT was performed in 1 patient, and MRI in 2 patients. Microscopic analysis was based on the resected specimen in all cases.

Results

All patients were symptomatic with respiratory symptoms in 4 cases, signs of heart failure in one and conscious trouble in the remaining patient. Four patients had a past medical history consistent with hypertension in 3 cases, renal failure in one (# 3) and diabetes mellitus in one case (# 4). Trans-oesophageal ultra-sound examination was performed in all patients and revealed a mobile mass located in the right atrium in one case and in the left atrium in 5 cases (Fig. 1a). CT was performed in one patient (# 1), and MRI was performed in 2 patients (# 4, 6). These investigations allowed to rule out a presumed thrombus and highlighted the possibility of a myxoma (Fig. 1b). All patients were treated surgically. The surgical approach consisted in a median sternotomy, and all tumours were completely resected. Gross features were similar in all cases and consisted in a gelatinous but non-friable lesion with a mean size of 20 mm (Fig. 1c). Microscopic features consisted in prominent spindle/ovoid/stellate cells organized around blood vessels, with a background of blue-grey mucopolysaccharide ground material (Fig. 1d). One patient died 72 hours after surgery due to an atrial arrhythmia, and one patient presented, immediately after surgical excision, with early atrial fibrillation that was treated successfully with medical treatment (# 3). None of the other patients had either early or late complications. Patient characteristics are shown in Table I.
Comments

Myxomas are by far the most common primary cardiac tumours. They may be sporadic or familial as part of Carney syndrome, which associates with spotty pigmentation of the skin, cutaneous myxomas, non-myxomatous extra-cardiac tumours and hyperendocrine states. Approximately 75-85% of cases occur in the left atrium cavity, 15-20% are located in the right atrium and only 5% in both atria as well as in the ventricles. Our study was particular because of the location of the myxoma in the right atrium in one case. The remaining tumours were located in the left atrium. Physical symptoms are non-specific due to endomyocardial flow obstruction or peripheral embolization. These symptoms may be summarized into obstructive cardiac signs, embolic signs (due to the friability of the mass itself) and systemic signs as a consequence of interleukine-6 release from the tumour cells (fever, flu-like symptoms or symptoms suggestive of connective tissue disease, weight loss) ². Patients with right atrial myxoma can present with right heart failure as a result of right ventricular outflow tract obstruction. Emboli in myxoma are not related to the size of the tumour, and can occur with a very small tumour even before mechanical interference ³. It is observed in 30-45% of patients, most frequently in the cerebral arteries ⁴. In our study, patient 1 presented conscious trouble. We may suppose that this sign was secondary to embolic tumour fragments in cerebral circulation. The other patients presented symptoms related to a heart failure. Four patients presented past medical history that was consistent with metabolic problems. This makes us wonder about the pathogenic significance of metabolic disorders in cardiac myxomas. In familial myxomas, a key role of the PRKAR1α gene has been demonstrated. This gene encodes the R1α subunit of protein kinase A. The R1α protein is known to be a critical enzyme in intracellular signal transduction that regulates all aspects of cell metabolism. R1α is a classic suppressor tumour gene, and many authors stipulate that the first hit is similar in familial and sporadic tumours, but the second hit may involve other genes. In our study, we describe sporadic tumours, but the presence of metabolic disorders in four patients may indicate the presence of mutations in the PRKAR1α gene because of its implications on cell metabolism ⁵. Trans-oesophageal ultra-sound examination is considered the gold standard diagnostic tool for initial assessment. It enables to localize the tumour in order to organize a surgical approach. Tumours appear as echogenic, mobile masses attached to the valve, the endocardial surface, or prosthetic materials in the heart. They frequently show high-frequency flutter or oscillation. Vegetations suggestive of infective endocarditis can also be detected ⁶. When trans-thoracic ultra-sound examination is non-conclusive, visualization can be enhanced by nuclear MRI or CT. Intravenous coronary angiography or CT angiography should be performed in older patients who are at risk for coronary artery disease and to enable concomitant coronary artery bypass ⁷. It

Table I. Patient characteristics.

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age at diagnosis</th>
<th>Gender</th>
<th>Symptoms</th>
<th>Trans-oesophageal examination</th>
<th>Surgical approach</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>F</td>
<td>Conscious trouble</td>
<td>Right atrial mass</td>
<td>Median sternotomy</td>
<td>Death (arrhythmia)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>Chest pain</td>
<td>Left atrial mass</td>
<td>Median sternotomy</td>
<td>Good (9 months)</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>F</td>
<td>Dyspnea</td>
<td>Left atrial mass</td>
<td>Median sternotomy</td>
<td>Good (12 months)</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>F</td>
<td>Palpitation</td>
<td>Left atrial mass</td>
<td>Median sternotomy</td>
<td>Good (2 years)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>Dyspnea</td>
<td>Left atrial mass</td>
<td>Median sternotomy</td>
<td>Good (5 years)</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>F</td>
<td>Heart failure</td>
<td></td>
<td>Median sternotomy</td>
<td>Good (1 year)</td>
</tr>
</tbody>
</table>

Fig. 1. a: Transthoracic echocardiography showing a large tumour in the left atrium, b: A chest CT scan with intravenous contrast showing an enlarged cardiac silhouette with intra-atrial hyper-density, c: Macroscopic appearance of an oval-shaped and gelatinous mass, d: Microscopic findings showing prominent spindle cells around blood vessels. These cells show no atypia or mitotic figures (HE x250).
was performed in two cases in our study who were aged 77 and 65-year-old (#3, 4). Some authors propose that cerebral CT or MRI scan should be performed before surgery in all patients with a cardiac myxoma, especially in those with left cardiac chamber localization because of the correlation of these tumours with cerebral aneurysm formation. Treatment is based on surgical removal. It must be performed without delay to reduce the risk of associated complications such as thrombo-embolic events, sudden cardiac death and to rule out a malignant tumour. In addition, it should be noted that atrial myxoma can have a rapid growth, varying from 1.3 to 6.9 mm per month. Resection should be complete, including all of the pedicle and area of attachment, plus a margin safety, followed by suture repair of the valve and annuloplasty. Surgical removal of myxoma is related to a low risk of mortality and early complications. Peri-operative mortality ranges from 0% to 7.5%. The most common post-operative complication, according to the literature, is arrhythmia (supra-ventricular premature contractions and atrial fibrillation). One of our patients, who had a left atrial myxoma, died three days after operation due to supra-ventricular arrhythmia. Final diagnosis is based on histologic examination. Microscopic findings consist in slender or plump “myxoma cells” forming nests, communicating cords and perivascular aggregates within a prominent myxoid matrix containing degenerative elastotic material, old haemorrhages and calcification. These tumours are benign; however, metastasis may occur from embolization from the primary tumour. Tumour recurrence is higher in young patients, in familial forms of myxoma and in multi-locular myxomas, and is estimated to be about 5%. Recurrences are generally observed during the first four years after surgery.

In summary, myxoma is the most common cardiac neoplasm. Due to varying symptoms, its diagnosis is frequently quite challenging. Surgical removal of these tumours is recommended without delay because of the possibility of multiple complications.

CONSENT SECTION
Written informed consent was obtained from the patients for publication of this case report and any accompanying images. Copies of the written consents are available for review by the Editor-in-Chief of this journal.

CONFLICT OF INTEREST
None declared.

References
Lung metastasis from TTF-1 positive sigmoid adenocarcinoma. Pitfalls and management

Introduction

Thyroid transcription factor-1 (TTF-1), a 38 kd homeodomain-containing DNA-binding protein, plays a critical role in the organogenesis of the lung, thyroid, ventral brain and pituitary gland. It was originally identified in follicular cells of the thyroid and subsequently in pneumocytes, making TTF-1 a reliable marker for differential diagnosis in distinguishing primary lung carcinoma and metastasis, especially when dealing with an adenocarcinoma or a large-cell carcinoma. It was generally thought that adenocarcinomas arising in the gastrointestinal tract do not express TTF-1. Recently, it has been reported that a small percentage (1.8%-5.8%) of intestinal adenocarcinoma TTF-1 positive show differences in sensitivity/specificity depending on the antibody clones. We report a case of lung localization of a TTF-1 positive adenocarcinoma in a patient with a history of colon adenocarcinoma. Based on the current results and previous reports, we propose the following criteria for diagnosing lung metastasis from TTF-1 positive intestinal adenocarcinoma.

1) Clinical features and anamnestic history are diagnostic milestones, and provide very important information as a prognostic parameter of primary carcinoma and the time interval between the two localizations (primary and metastasis).
2) The histologic features are compatible with an enteric differentiation.
3) TTF-1 must be tested in the primary carcinoma.
4) In lung lesions, in association with TTF-1, it could be useful to test other immunohistochemical markers such as CDX-2 and NapsinA.
5) Testing other immunohistochemical or molecular markers in either lesion is not very useful. Heterogeneity between primary and metastatic lesions has been reported in the literature. Application of the above-mentioned criteria would simplify diagnosis of lung metastases from TTF-1 positive intestinal adenocarcinoma.

Case report

In 2012, a 55-year-old woman with a history of colonic adenocarcinoma presented with a left lung mass associated with mediastinal lymphadenopathy. The clinical features suggested exclusion of a lung origin carcinoma. The endoscopic biopsy showed an adenocarcinoma with enteric features. The immunohistochemistry profile showed widespread positive staining in neoplastic cells for the following markers: TTF-1, CDX-2 and CK20, while CK7 was negative. A strong expression of MLH-1, MSH2, MSH6 and
PMS2 proteins was noted in neoplastic cells, associated with no mutations (“wild-type”) in exon 1 of the *KRAS* gene.

The sigmoid carcinoma was removed in 2009 by left hemicolectomy. Grossly, the tumour measured 3.5 cm (longitudinal) x 3 cm (transversal) and was located in the left colon (sigma/rectum), involving the perivisceral fat tissue (pT3). It presented as a well-demarcated mass that was 2 cm from the rectal surgical margin. Histologically, the tumour was a carcinoma consisting of a moderately differentiated (G2) glandular component with low level tumour budding associated with a massive vascular invasion. Metastases were observed in regional lymph nodes (6/16)(pN2). The patient underwent adjuvant chemotherapy. In 2012, the immunohistochemistry of this lesion showed strong widespread expression of TTF-1 (Fig. 3), CK20, CDX-2, MLH-1, MSH2, MSH6 and PMS2 in neoplastic cells. No mutation was found in exon 1 of the *KRAS* gene (“wild-type”).

**Methods**

Specimens were fixed in 10% neutral buffered formalin, paraffin-embedded, sectioned, and stained with haematoxylin and eosin. The antibodies used (with their clones, dilutions, antigen retrieval, and manufacturer) included: Cytokeratin 20 (Ks20.8, prediluted, Bond Enzyme Pre-treatment Kit, Novocastra Laboratories, Newcastle, UK); Cytokeratin 7 (OV-TL 12/30, 1:100, Bond Epitope Retrieval Solution 1, Novocastra Laboratories, Newcastle, UK); CDX-2 (DAK-CDX-2, 1:25, Bond Epitope Retrieval Solution 2, DAKO, Cambridge, UK) MLH1 (ESO5, 1:100, Bond Epitope Retrieval Solution 1, Novocastra Laboratories, Newcastle, UK); MSH2 (25D12, 1:80, Bond Epitope Retrieval Solution 2, Novocastra Laboratories, Newcastle, UK); MSH6 (44, 1:25, Bond Epitope Retrieval Solution 1, Cell Marque Rocklin, USA); PMS2 (MRQ-28, 1:20, Bond Epitope Retrieval Solution 2, Cell Marque Rocklin, USA); TTF-1 (SPT-24, prediluted, Epitope Retrieval Solution 1, Novocastra Laboratories, Newcastle, UK). Markers were detected with a polymeric-labelling two-step method (Bond Polymer Refine Detection) in an automated staining system Bond-maX (Leica Biosystems, Newcastle, Ltd.).
Molecular analyses were performed using a Chromo4 Real-Time PCR Detection System (Bio-Rad Laboratories, Segrat, Milan, Italy). Analyses of KRAS gene mutations were performed on DNA extracted from formalin-fixed, paraffin-embedded tissue. After histological examination, tumour was scraped from 10 μm-thick sections and genomic DNA was then extracted by using QuickGene SP DNA tissue kit (Fujifilm Corporation, Life Science Products Division, Minato-ku, Tokyo, Japan) according to the manufacturer’s instructions. Exon 1 of the KRAS gene was amplified by PCR with a set of appropriate primers. We tested the case in two templates with a case-control for the status “wild-type” and a case-control for each mutation studied.

Discussion

The lung is a frequent site of metastatic involvement, and in many cases differential diagnosis between a metastasis and primary carcinoma is a substantial question. In these cases, the clinical features and anamnestic history are keys factors for diagnosis in association with information from histologic evaluation. Nevertheless, when clinical features are doubtful immunohistochemical or molecular tests are needed in clarifying the origin of the carcinoma. TTF-1 is one of the most reliable markers to answer this question. Two main commercially-available clones of monoclonal antibodies have been developed against TTF-1 for immunohistochemical use: 8G7G1/1 and SPT24. When comparing the immunostaining profile of primary lung adenocarcinoma with these two antibodies, the literature reports that the SPT24 clone is much more sensitive than the 8G7G1/1 clone with a positive rate of 84% and 65%, respectively. Although the TTF-1 SPT24 clone has a stronger affinity for lung adenocarcinoma, it may lead to a few TTF-1 positive non-pulmonary carcinomas such as ovarian, endometrial and small-cell carcinoma. It was generally thought that adenocarcinomas arising in the gastrointestinal tract do not express TTF-1. Recently however, it has been reported that TTF-1 positive intestinal adenocarcinoma range 1.8% to 5.8%, with higher positivity with the SPT24 clone over the 8G7G1/1 clone. The role of TTF-1 in colorectal neoplastic pathogenesis is not dominant and still unclear, and further investigations are mandatory. It is possible that TTF-1 may be aberrantly expressed in a few colorectal carcinomas as a consequence of somatic genetic alteration or amplification of the chromosomal region including the TTF-1 gene. As such, association with the site of primary carcinoma should be interesting to study as both cases reported are of sigma/rectum origin.

We report a case where the clinical features (lung neoplasia associated a mediastinal lymphadenopathy three years after left hemicolectomy) prompted us to test a bronchial biopsy by immunohistochemistry. The specimens showed diffuse positivity for TTF-1, CDX-2 and CK20 in neoplastic cells. The differential diagnosis was between a colonic metastatic lesion versus enteric-type pulmonary adenocarcinoma. In the literature, there are no previous reports of an enteric-type pulmonary adenocarcinoma arising in a patient with a colonic carcinoma. The low incidence of diagnosis suggested the possibility of a metastasis, and TTF-1 expression in sigmoid carcinoma confirmed this hypothesis.

Based on the information obtained from the current and previously-reported cases, we propose the following criteria when establishing a diagnosis of lung metastasis from TTF-1 positive intestinal adenocarcinoma. 1) Clinical features and anamnestic history are diagnostic milestones, and provide very important information on the time interval between the two localizations and prognosis of primary carcinoma. The patient must have a history of intestinal carcinoma and clinical imaging suggesting a metastasis. In theory, the primary intestinal carcinoma could be occult. 2) The histologic features are compatible with an enteric differentiation. The slides of lung neoplasia must be compared with the slides of primary intestinal carcinoma. 3) TTF-1 must be tested in the primary carcinoma. 4) In lung lesions, in association with TTF-1, it may be useful to test other immunohistochemical markers such as CDX-2 and NapsinA. It is worthwhile noting that immunohistochemical study in cases clearly diagnosed as metastases could lead to delays in therapy. 5) To test other immunohistochemical or molecular markers in both lesions is not very useful. In the current case, MMR (MLH1, MSH2, MSH6 and PMS2) and KRAS were similar in both lesions, but heterogeneity between the primary tumour and metastasis has been reported in the literature. We suggest testing these markers only in the case in which TTF-1 in the primary carcinoma is negative. The application of these criteria would simplify diagnosis of lung metastases deriving from TTF-1 positive intestinal adenocarcinoma.

References


Introduction

Tuberculosis is a common infectious disease in developing and underdeveloped countries. Primary tuberculosis of adenoids is rare and only few cases have been reported worldwide. Herein, we present a case of primary tuberculosis of adenoids presenting with hypertrophy of adenoids and hearing loss.

Case report

An 11-year-old boy with a two year history of snoring and gradual left ear hearing loss was admitted to outpatient otolaryngology clinic. He had low grade intermittent fever during this period. There were neither respiratory symptoms nor otorrhoea or otalgia. The patient had a past history of favism (glucose-6-phosphate dehydrogenase deficiency), but there was no previous history of haemolytic crisis, signs or symptoms or laboratory tests that would indicate immunodeficiency. In physical examination tonsils size were in grade 1, and anterior rhinoscopy was normal. Otoscopy revealed a severe retracted tympanic membrane in the left ear, but the right ear was normal. There was no lymphadenopathy. Lung auscultation and chest X-ray were clear. No organomegaly was detected. The patient underwent adenoidectomy, and myringotomy was also carried out on left ear. There was no glue or secretion, but because of the severely retracted tympanic membrane, a ventilation tube was inserted.

Pathologic features

The resected adenoid specimen consisted of multiple pieces of creamy colored tissues, in total 3 x 2.5 x 1 cm (Fig. 1). Microscopic study revealed lymphoid tissue that was involved by numerous granulomatous lesions with central caseating necrosis and multinucleated giant cells both Langhans and foreign body types (Fig. 2); tuberculosis was suggested. At Ziehl-Neelsen staining a few acid-fast bacilli were present (Fig. 3). PCR also was done on the specimen, and the result was positive.

The patient was visited 10 days after surgery. Snoring was decreased, there was no otorrhoea or any complication of left ear, but multiple lymphadenopathies were detected at anterior jugular and posterior triangle lymph nodes bilaterally. Chest X-ray was normal (Fig. 4). The patient continued to have low-grade fever during this time. Based on pathological and clinical findings, he was hospitalized and received anti-tuberculosis treatment that was continued and completed af-
Discussion

Tuberculosis is a common infectious disease caused by Mycobacterium tuberculosis, which affects mostly the lungs although other parts of the body may also be involved. The immune system of body reacts to Mycobacterium tuberculosis infection with a type four hypersensitivity reaction, which is specified by caseating granulomatous inflammation due to activation of CD4+ T-helper cells and macrophages. The main source of Mycobacterium tuberculosis infection is the respiratory tract, so that adenoids can be infected by bacteria when they pass through the nasopharynx (adenoid tuberculosis secondary to respiratory tuberculosis). Primary tuberculosis of adenoids is rare, and although in some reports the incidence of tonsillar involvement has been estimated at about 70%, only a few cases of primary tuberculosis of adenoids have been reported. Van Lierop et al. reported one case of adenoid tuberculosis among 172 adenoidectomies and tonsillectomy specimens, and also mentioned that in developed countries like United States primary tuberculosis was much more rare than in Thai and Chinese patients. It seems that elderly patients with immunodeficiency are more prone to oral tuberculosis. Tuberculosis of lungs is associated with classic symptoms such as fever, night sweating, blood–tinged sputum, chronic cough and weight loss, but it appears that tuberculosis of adenoids does not have such specific symptoms.

Mahindra et al. reported three cases with primary tuberculosis of tonsils and adenoids with enlargement of cervical lymph nodes, but in our patient there was no enlargement of cervical lymph nodes before adenoidectomy. Diagnosis of tuberculosis is based on chest X-ray and tuberculin skin test, and in cases for whom the chest X-ray is clear and there are no respiratory sign or symptom, primary tuberculosis is considered. Caseating granulomatous inflammation in biopsy specimens suggest tuberculosis that can be confirmed by Ziehl-Neelson staining. Many other conditions such as sarcoidosis and Wegener’s granulomatosis can be involved in differential diagnosis of granulomatous inflammations. In sarcoidosis, the granulomas does not have a central caseating necrosis, and in Wegener’s granulomatosis, the patient has vasculitis with a positive C-ANCA (cytoplasmic antineutrophilic cytoplasmic antibodies) test (our patient showed a negative result for C-ANCA) and Ziehl-Neelson staining is negative both in Wegener’s granulomatosis and sarcoidosis. The most common symptoms in adenotonsillar tuberculosis are hearing loss, otalgia, cervical lymphadenopathy and nasal discharge. Our patient had only hearing loss, low-grade fever and snoring at the time of admission.
Conclusion

Despite the rarity of primary tuberculosis of adenoids, it should be considered in the differential diagnosis in patients with hypertrophy of adenoids, especially in developing and underdeveloped countries, and must be studied pathologically for definitive diagnosis.

References

Memoir of Antoine Zajdela

Antoine Zajdela is no longer with us. Antoine, a teacher and a friend. A person who gave me a lot with his knowledge and wisdom, but also with his simplicity and his example. He is one of the persons I met in the scientific community world that I felt more of a friend. It was easy to talk about everything with him: he slipped naturally from the academic conversation to social or human or personal issues. I learned of his full life by him, of his childhood spent in Slovenia, the country where he was born, his medical studies at the University of Padua and his arrival in Paris where he joined his brother, who was also a doctor. I also learned from him how he started his forefront research, in the context of fine needle aspiration cytology. Antoine insisted on the importance of sampling by the cytopathologist in person and this approach gave a decisive contribution to cytopathology as a field of pathological Anatomy, especially in the breast diagnostics. At Curie Institute, where he worked for about 40 years, his prestige was such that a Cytopathology service had been created for him and his activity, not separated by Histopathology, of which he was director.

I met Antoine about 35 years ago. I knew he loved to come often to visit Italy because he had a small apartment in Venice. We decided to organize Cytology courses at the University of Trieste. Those courses became annual and many young Cytologists joined with interest the appointment in Trieste. Those 21 years of constant editions of courses, became an opportunity for many colleagues to have a chance to do an experience of studying in Paris. The human qualities of Antoine showed through the teaching and represented a milestone for his students. He was able to transmit as the most complex diagnosis could often be solved with a rigorous but simple reasoning. He was the one who made many Italians love cytology and lots of us owe him a lot. In my case, he encouraged me to share the courses of Trieste and overcome my fears, then inviting me to repeat them in Paris. Without his encouragement I would not have received the rewards I got later in my academic life. Françoise, his wife, also became a constant presence in our meetings. Whenever I called Antoine in Paris, we were always happy to gather: in their home or in some bistros. Then over time some of his students like Philippe Vielh and later on Jerzy Klijnianienko joined our scientific meetings. Names that are nowadays well known in the international field.

One of the things I still remember like it was today is how much Antoine cared for seeing the publication of the handbook and atlas of Mammary Cytology that Piccin published in 1995. I also remember his joy when SIAPEC (Italian Society of Anatomic Pathology and Cytology) counted him among its honorary members. My mind is full of vivid memories of Antoine, as a teacher and as a friend. I want to just tell Him thanks with all the humanity that he taught me. I’m sure, there are many others, like me, who will not be able to and who will not want to forget it.

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