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Case report

Solitary thyroid metastasis from colon cancer: fine-needle aspiration cytology and molecular biology approach

M. ONORATI[1], P. UBOLDI[1], C.L. BIANCHI[1], M. NICOLA[1], G.M. CORRADINI[2], S. VERONESE[3], A.I. FASCÌ[4], F. DI NUOVO[1]
[1] Pathology Unit, Garbagnate Milanese, AO "G. Salvini" Garbagnate Milanese, Italy; [2] Oncology Unit, Garbagnate Milanese, AO "G. Salvini" Garbagnate Milanese, Italy; [3] Molecular Pathology Unit, Department of Laboratory Medicine, Niguarda Cancer Center, Milan, Italy; [4] Surgical Unit, Garbagnate Milanese, Italy

Key words

Solitary thyroid metastasis • Fine needle aspiration cytology • Colon cancer

Summary

Thyroid gland is one of the most vascularized organs of the body, nevertheless clinical and surgical series report an incidence of secondary malignancies in this gland of only 3 %. Colorectal carcinoma metastatic to the thyroid gland is not as uncommon as previously believed, infact the number of cases seems to be increased in recent years due to the more frequent use of fine-needle aspiration cytology (FNAC) guided by ultrasonography. Although kidney, breast and lung metastases to the thyroid are frequent, metastasis from colon cancer is clinically rare with 52 cases reported in the literature in the last 5 decades and three cases described as solitary thyroid metastasis from the colon cancer without any other visceral metastases.
To the best of our knowledge, we report the fourth case of solitary, asymptomatic thyroid metastasis from colon cancer without involvement of other organs. We discuss the importance of FNAC to detect metastatazing process as a compulsory step of the diagnostic and therapeutic management algorithm, combined with a molecular biology approach. A review of the last 5 decades literature, to update the number of cases described to date, is also included.

Introduction

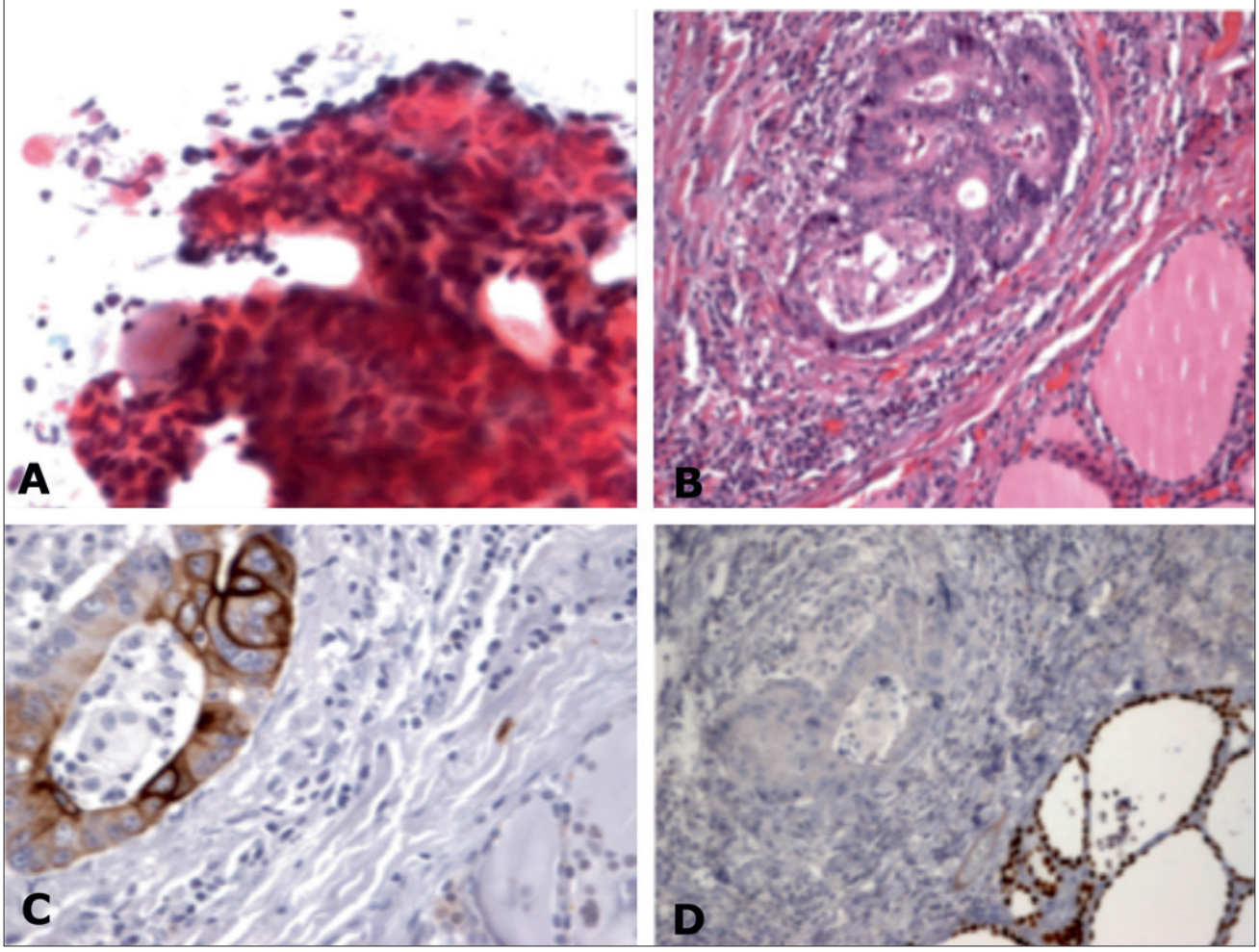
Colon cancer is one of the most common cancers with a high propensity to metastasize to the regional lymph nodes, the liver and the lung. Colon cancer metastasis to the thyroid gland is uncommon. Infact, they have been assessed originating mainly from renal, lung and breast carcinoma. In this regard, routine evaluation of thyroid nodules by FNAC in patients with primary known cancer may increase detection of metastatic lesions with increasing frequency. In this report we describe a case of colon carcinoma metastatic to the thyroid gland without involvement of other organs, diagnosed by FNAC 26 months from the primary malignancy. Combined cytology with histology, immunostaining and molecular biology analysis has been the best and complete diagnostic and therapeutic approach to the metastatic disease.

Case report

In January 2010, a 51-year-old woman underwent a left colectomy. A moderately differentiated colon adenocarcinoma was histologically diagnosed (pT3N2a). From March 2010 to August 2011 the patient received 12 cycles of chemotherapy with FOLFOX4 (Oxaliplatin + 5 fluorouracil + folic acid). The patient has been free from disease for 26 months when she noted a slight enlargement of the right lobe of the thyroid so that in October 2013 she underwent a routine ultrasound examination that revealed a solid and hypoechogen nodule with an unclear border, measuring 10 mm in maximum diameter. Enlargement of cervical lymph nodes was not evident. The laboratory data revealed no abnormalities in CEA levels and in thyroid function. Ultrasonography-guided FNAC of the thyroid nodule was performed using a 22-gauge needle attached to a disposable 10-ml plastic syringe. Thyroid aspiration cytology was hypercellular and showed

Correspondence
Monica Onorati, Pathology Unit, Garbagnate Milanese, A.O. "G. Salvini" viale Carlo Forlanini 121, 20024 Garbagnate Milanese, Italy - Tel. +39 02 994302632 - E mail: monica.onorati@libero.it

Fig. 1. A) Fine-needle aspiration cytology of the thyroid nodule: neoplastic cells form a large sheet. Note the colloyd globules near the neoplastic sheet. **B)** Histological findings showing metastasis from carcinoma of the colon to the thyroid: note both normal thyroid follicles and colonic carcinoma. **C)** Immunohistochemical expression of CK20 in the neoplastic cells. **D)** Immunohistochemical expression of TTF-1 in normal thyroid follicles.

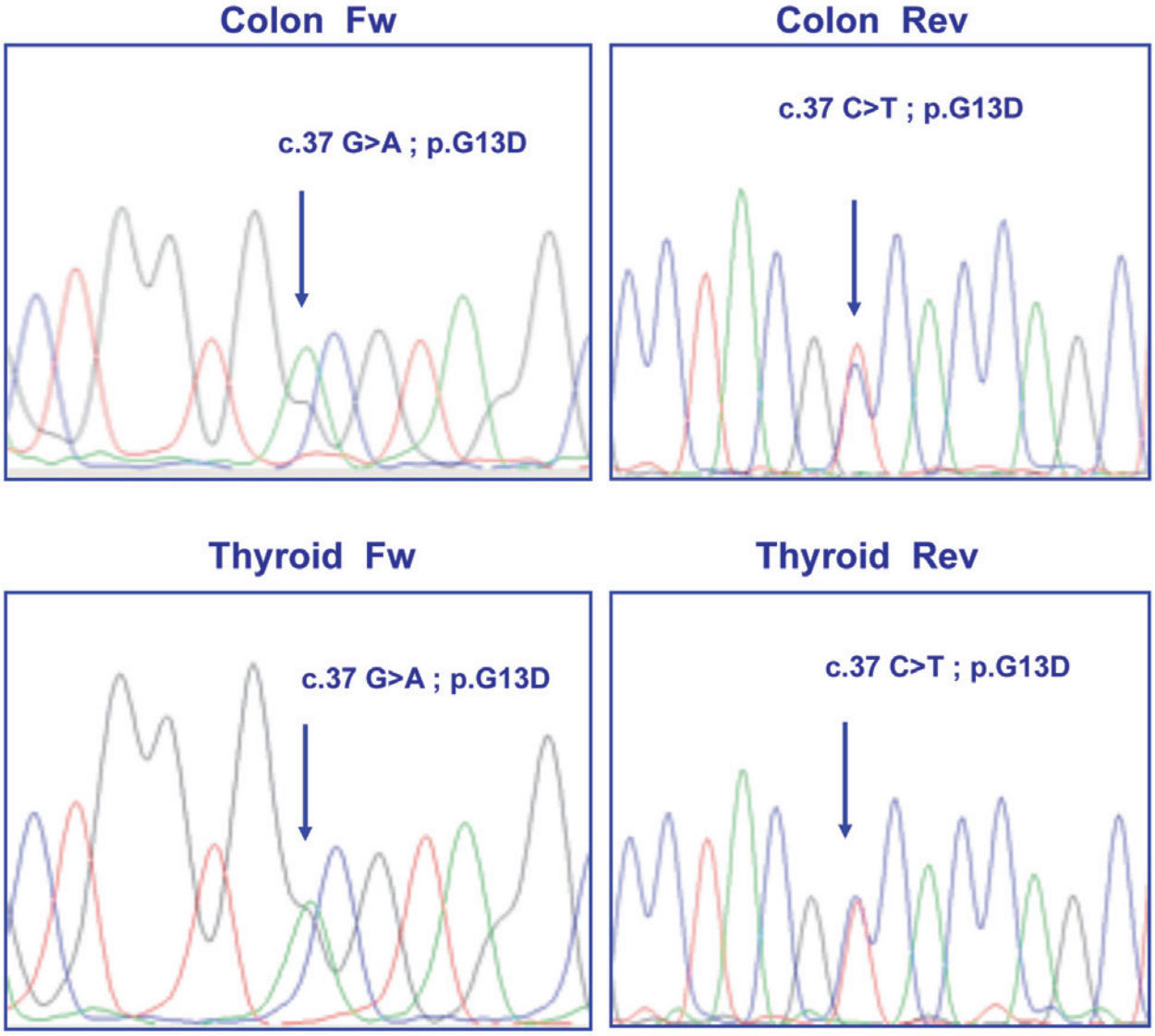


clusters of malignant tall columnar cells with a high degree of cell overlapping with some colloid globules and necrosis intermingled to neoplastic cells (Fig. 1a). Based on these cytological features and the clinical history, a diagnosis of thyroid metastasis from colon cancer was formulated. At the end of March 2014, a total thyroidectomy was performed. On gross examination, the right lobe of the thyroid was slightly enlarged and the cut surface showed a whitish, solid nodule. Microscopically, the malignant cells showed cribriform glandular structures covered by cuboidal cells (Fig. 1b). The immunohistochemical positivity for Cytokeratin 20 (CK20) (Fig. 1c) and CDX2 (Fig. 1d), associated to the negativity for TTF1 and Cytokeratin 7 (CK7) confirmed the intestinal etiology as diagnosed by FNAC.
Tissue samples from primitive (colon) and metastatic (thyroid) tumors were microdissected and DNA purification was performed using QIAamp DNA FFPE Tissue Kit (Qiagen) according manufacturer's instructions. Molecular analyses revealed the presence of the same p.G13D mutation (G > A) in codon 13 of exon 2 of KRAS gene in both tumors, determining the substitution of a Glycine with an Aspartic Acid, in both surgical specimens (Fig. 2). According to this molecular data, following surgery, the patient underwent chemotherapy with FOLFIRI (irinotecan + 5 fluorouracile + folinic acid) without the addiction of cetuximab. The postoperative course was uneventful and the patient is still alive 18 months after thyroidectomy, without any other evidence of disease.

Discussion

The number of clinical papers reporting carcinomas metastatic to the thyroid is extremely limited. In 1960, among the 58 cases collected by Elliot [1], the most common metastatic tumor to the thyroid gland was renal carcinoma (33 cases) followed, in order, by gastrointestinal tract, lung and breast cancer.
According to a report by Wychulis et al [2], in 1964 there were only 10 cases (0.05 %) of tumor metastasis to the thyroid out of 20.262 cases involving thyroid surgery. In 1987 Ivy [3] reported the Mayo Clinic statistics, accord-

Fig. 2. Sequencing electropherograms (forward + reverse) of colon cancer and metastasis to the thyroid gland showing the mutation in codon 13 of the KRAS gene.



ing to which, only 30 cases of thyroid metastasis were observed over a 36 years period.

Most of these cases were renal, breast, and lung cancers, which had a similar rate of occurrence. According to Mayo Clinic reports [4], in 1997 43 cases were observed in a 10 years period, and the most frequent primary tumors were again renal, breast, and lung cancer. Conversely, there are few clinical reports of metastasis of colon cancer to the thyroid. Regarding the reason why thyroid metastasis from other primitive tumors are generally uncommon, two hypotheses were formulated by Willis [5] and supported for a long time. One "mechanical" hypothesis refers to the extremely abundant supply of arterial blood to the thyroid, and its fast blood flow, which make difficult the adhesion and implantation of tumor cells in the gland. Another "chemical" explanation could be that the high oxygen saturation and high iodine content of thyroid tissues inhibits the growth of tumor cells. Regarding the latter, Smith et al. [6] argued that, when an organic disorder exists in the thyroid tissue, a decrease in arterial blood flow and a low-oxygen or low-iodine state results, thus increasing the susceptibility to metastasis. Also, the route of metastasis is believed to be haematogenous, through portal, pulmonary, and large veins, therefore metastasis to the lungs or liver often occur prior to thyroid metastasis, although the latter sometimes occur directly without prior involvement of lung or liver.

As a route in this case, the existence of a vertebral venous system has long been suggested, and this theory can explain metastasis to the thyroid from mammary glands, kidneys or pelvic organs [7]. Thyroid gland metastases from colonic carcinoma are clinically rare probably because FNAC guided by ultrasonography was not used as preoperative diagnostic procedure in past years. The number of clinical cases with metastasis of colon cancer to the thy-

Tab. I.

No.	Reported year and authors	Age/Sex	Primary site	Free interval after colectomy	FNA	Prognosis
1	CURRENT CASE	51/F	LC	45 m	Done	Alive
2	COZZOLINO et al.[23] 2010	66/M	SC-R	6	Done	-
3	HYUN et al.[22] 2010	59/F	AC	6 m	Done	-
4	YOUN et al.[21] 2006	85/M	R	21 m	Done	-
5	CAVANNA et al.[20] 2006	55/F	SC	24 m	Done	2 DOD
6	MATTAVELLI et al.[19] 2006	52/F	R	30 m	Done	Alive
7	HANNA et al.[18] 2006	28/F	COLON NOS	-	Done	-
8	FADARE et al.[17] 2005	59/F	SC	-	Done	Alive
9	RIDDER et al.[11] 2005	75/F	SC	85 m	Not Done	12 DOD
10	HAKER et al.[16] 2005	77/M	-	84 m	Not Done	Alive
11	KOKLU et al.[15] 2005	64/F	-	Concurrent	Done	-
12	MALANI et al.[14] 2005	49/F	R	12 m	Not Done	7 DOD
13	PHILLIPS et al.[13] 2005	81/F	COLON NOS	-	Done	-
14	POON et al.[12] 2004	64/M 53/F	R SC	12 m 1 m	Done Not done	18 DOD 10 DOD
15	FUJITA et al.[11] 2004	28/F	R	Concurrent	Done	6 DOD
16	WITT et al.[10] 2003	71/M	R	7 m	Done	-
17	ROSSI et al.[9] 2003	42/M	LC	-	Not Done	-
18	PERINU et al.[11] 2003	43/M	LC	24 m	Not Done	Alive
19	KUMAMOTO et al.[8] 2003	66/F	AC	3 m	Done	4 AWD
20	YAMADA et al.[8] 2003	60/F	R	3 m	Done	4 DOD
21	OGISAWA et al.[8] 2002	58/M	R	-	Done	-
22	AKIMARU et al.[8] 2002	67/M	AC	6 m	Done	4 DOD
23	KANAYA et al.[8] 2001	80/F	AC	1,5 m	Done	OTHER DEATH
24	BOLEAS et al.[11] 2001	80/F	COLON NOS	7 m	-	-
25	SHIGA et al.[8] 2001	36/F	R	3 m	Done	2 ALIVE
26	SHINOHARA et al.[8] 2000	66/F	TC	4 m	Not Done	4 AWD
27	KIM et al.[8] 1999	68/F	SC	2 m	Done	6 AWD
28	TAZUKE et al.[8] 1998	61/F	R	2 m	Not Done	Alive
29	TAKASHIMA et al.[8] 1998	67/M	R	2 m	Done	-
30	NAKAMURA et al.[8] 1997	70/F	AC	5 m	Done	6 DOD
31	YOSHIMATSU et al.[8] 1996	50/F	AC	0,5 m	Done	5 DOD
32	MASUDA et al.[8] 1996	38/F	R	4 m	-	5 DOD
33	MASUDA et al.[8] 1996	73/M	R	1 m	-	Alive
34	OSIN et al.[8] 1996	70/F	SC	Concurret	Done	AWD
35	MASE et al.[8] 1993	-	SC	4 m	-	-
36	SHIBUTANI et al.[8] 1992	52/F	SC	3 m	Done	8 DOD
37	MAEDA et al.[8] 1992	66/F	AC	1 m	Done	2 AWD
38	MATSUSAKO et al.[8] 1991	78/F	AC	1 m	Done	-
39	JINGU et al.[8] 1990	48/F	R	2,5 m	-	10 DOD
40	CRISTALLINI et al.[8] 1990	64/F	-	4 m	Done	12 AWD
41	MESKO et al.[8] 1990	59/F	R	2 m	Done	-
42	RIGAUD et al.[8] 1987	68/F	-	2 m	-	3 DOD
43	RIGAUD et al. [8] 1987	77/M	R	4 m	-	1 DOD
44	LESTER et al.[8] 1986	55/F	AC	2,5 m	Not Done	-
45	IVY et al.[3] 1984	72/M	-	192 m	Not Done	< 12 DOD
46	ITO et al.[8] 1983	34/M	R	2 m	Done	7 DOD
47	ISHIDA et al.[8] 1982	70/F	R	concurrent	Not Done	3 DOD
48	MAKE et al.[8] 1974	68/M	SC	4 m	Done	8 DOD
49	WYCHULIS et al.[1] 1964	37/F	R	0,5 m	-	10 DOD
50	ELLIOTT et al.[2] 1960	56/F	R	concurrent	-	3 DOD
51	SKLAROFF et al.[8] 1954	73/F	R	7 m	-	2 DOD

NOT AVAILABLE; F: female; M: male; m: months; AWD: alive with disease; DOD: dead of disease; FNA: fine-needle aspiration; RC: right colon; LC: left colon; AC: ascending colon; R: rectum; TC: transverse colon; SC: sigmoid colon

roid, to the best of our knowledge, was about 52 (obtained by systemic review of publication), including the present one (Tab. I) [1-23]. For our diagnosis, FNAC was performed similarly to ordinary thyroid testing, and was considered a useful procedure because it could diagnose metastasis from colon cancer as other cases. Therefore, the final treatment policy should be determined considering the level of metastasis to other organs, the patient's general condition, the presence or absence of local pressure symptoms, etc. In the present case, there was no evidence of metastases other than in the thyroid, so the thyroid was surgically ablated to reduce the dissemination and prevent local pressure symptoms that were prospected to occur in the future. Although thyroid gland metastasis from gastrointestinal tract cancer is mainly associated with the spread to other organs, in our case the presence of a solitary metastasis supports the theory of isolated spread to the thyroid via vertebral venous system bypassing the lung and the liver and associated with a better prognosis for the patient, as in our case.

Moreover it is important to keep in mind that the thyroid gland can be a site of metastases for a variety of tumors when evaluating a thyroid nodule [24-26], especially in a patient with a prior history of malignancy. For this reason physician should consider the possibility of thyroid gland metastasis when he is performing routine follow-up examinations for recurrence of colorectal cancer until proven otherwise. In the presence of a thyroid nodule, the first approach to the diagnosis must be the use of FNAC guided by ultrasonography. In fact the number of cases seems increased in recent years and this increase may be related to more frequent use of FNAC in any suspected case. The management of thyroid metastases should depend on the individual situation. FNAC helps to evaluate the right treatment avoiding unnecessary thyroidectomy in patients with a poor prognosis. In our case combined cytology together with histology, immunostaining and molecular biology analysis, has proved to be the most complete and efficient diagnostic and therapeutic approach to improve the disease free survival.

In medical centers with a wide range of clinical cases and a consolidated experience, FNAC remains a fundamental tool and plays a pivotal role in the diagnostic management and in the follow-up of malignancies because it is sensitive, repeatable, not invasive, and inexpensive. Finally molecular biology analysis performed on cytological specimen could help for an immediate therapeutic approach.

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