

# Primary thyroid biphasic synovial sarcoma and synchronous papillary carcinoma: report of a remarkable case

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## Key words

Biphasic synovial sarcoma • Papillary carcinoma • Molecular biology

## Summary

Synovial Sarcoma (SS) is the fourth most common soft tissue sarcoma, characterized by translocation t(X;18) (p11.2;q11.2). Although its histological features have been extensively described, this entity is characterized by a wide morphological spectrum so that the recognition can be very challenging at atypical anatomical localization, like the thyroid. We describe a case of a 42-year-old female patient complaining a cervical swelling due to left intrathyroid nodule, measuring 35 mm in its greatest dimension. A Fine Needle Aspiration Cytology (FNAC) was performed and diagnosis of indeterminate neoplastic lesion, indefinite whether primary or metastatic, was formulated. After complete thyroidectomy, the histological picture of the nodule was characterized by a

dual cellular population: several glandular structures composed by columnar cells with clear cytoplasm were embedded in a highly cellular stroma composed of spindle-shaped elements. Immunohistochemistry and molecular biology confirmed the morphological suspicion of SS identifying the fusion transcript SYT-SSX1 and thus ruling out several differential diagnoses which include more common thyroid malignancies. Moreover a synchronous papillary microcarcinoma was detected in the controlateral lobe. This case is noteworthy since it describes the synchronous presence in the thyroid of two completely different malignancies, the first one belonging to the soft tissue neoplasm category and the other one originating from the thyroid follicular epithelium.

## Introduction

Synovial Sarcoma (SS) is the fourth most common soft tissue sarcoma accounting for 5-10% of these neoplasms and is characterized by translocation t(X;18) (p11.2;q11.2) between the genes SYT and SSX1/SSX2/SSX4<sup>1,2</sup>. It usually arises in children and young adults in the extremities, especially around large joints<sup>1,2</sup>. The diagnosis of SS can be quite straightforward especially in prototypical cases arising at common locations. However at unusual locations or at atypical age groups achieving a diagnosis of SS may be challenging because of wide spectrum of differential diagnoses. In this setting primary thyroid SS is extremely rare with only a few cases reported in the English Literature even if the head and neck region represents one of most common site of SS origin<sup>1-7</sup>. However immunohistochemical and molecular analysis for t(X;18) can be routinely performed and therefore can help supporting the morphological hypoth-

esis. This report describes a case of primary thyroid SS in an adult woman. We would like to discuss potential diagnostic pitfalls due to the overlapping of histological features between SS and other primary and secondary thyroid malignancies.

## Case report

A 42-year-old female patient was referred to our Hospital for a left cervical swelling. Her previous medical history was unremarkable. She performed an ultrasonography evaluation (US) of the thyroid revealing, in the left lobe, an isoechoic nodule, with a hypoechoic rimming, measuring 35 mm in its greatest dimension and characterized by central and peripheral vascularization, without calcifications. All laboratory tests, including thyroid functional markers, were within usual ranges. The patient underwent an US-guided FNAC and a cyto-

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logical diagnosis of neoplastic lesion, indefinite whether primary or metastatic, was formulated. The patient underwent a total body Computed Tomography (CT) scan, revealing no other neoplastic lesion. A complete thyroidectomy was performed. During the surgical procedure the capsule of the left nodule was ruptured and grayish tissue fragments were discharged and collected for histological examination. The postoperative period was uneventful and the patient is alive and free of disease and has actually no other localization since two years.

## Materials and methods

The surgical specimens were fixed in 10% buffered formaldehyde and then routinely processed. Sections were stained with H&E. Immunohistochemical studies were performed using the following panel of antisera: cytokeratin 7, Bcl2, calponin, EMA, CD99, CD56, vimentin, Ki67, WT1, NSE, synaptophysin, calretinin, D2-40, CD5, pS100,  $\alpha$ fetoprotein, CD10, p63, PGR, ER, cytocheratin 20,  $\alpha$ -inhibin, LCA/CD45, Ca125, SMA, CD117, thyroglobulin (Ventana), TLE1 (Santacruz) and PAX8 (Proteintech). Fluorescence in situ hybridization (FISH) and REAL-TIME PCR (RT-PCR) analyses were performed on formalin-fixed and paraffin-embedded tissues (FFPE) from the surgical specimen of the thyroid neoplasm. A commercially available break-apart dual-color specific probe at 18q11.2 (Vysis-Abbot) for SS18 (SYT) gene rearrangement was applied according to manufacturer's instructions. Dual Color FISH images were digitally generated using a computer-based imaging system (Cytovision). As for RT-PCR, Total RNA was isolated from FFPE samples using the TRIzol reagents. Two  $\mu$ g of total RNA was reverse-transcribed into cDNA using oligo(dt) primers and reverse transcriptase (Superscript), according to the manufacturer's recommendations. The integrity of cDNA was tested by the amplification of the ubiquitous gene  $\beta$ -actine. The detection of the putative SYT-SSX1 and SYT-SSX2 fusion gene was carried out with the primers SYT 1100 5'AGGATATAGACCAACACAGCC3', SSX1 5'GGT GCA GTT GTT TCC CAT CG3' and SSX2 5'GGC ACA GCT CTT TCC CAT CA3'. PCR conditions were the following: 40 cycles of denaturation at 94°C for 30 sec, annealing at 58°C for 30 sec, and elongation at 72°C for 30 sec. Each reaction included cDNA from normal mesenchymal tissue as negative control. The amplification products of all the PCR reactions were analyzed on 2% agarose gel. All the sequence reactions were carried out using an automated sequencing system (3500 DX Genetic Analyzer, Applied Biosystem) following standard protocols.

## Pathological, immunoistochemical and molecular findings

On histological evaluation of the nodular lesion, a dual cellular population was appreciated: several glandular

structures composed by columnar elements with clear cytoplasm were embedded in a highly cellular stroma (Fig. 1A). Stromal cells were spindle-shaped, with scant cytoplasm and ovoid nuclei (Fig. 1A). Vessels had thin walls and a hemangiopericytoma-like appearance. Areas of necrosis and a high mitotic count were also detected. The tumor was surrounded by a thick fibrous capsule and did not infiltrate the nearby thyroid parenchyma (Fig. 1B). Immunohistochemical analysis showed a complex pattern: CD99 was expressed by spindle and epithelial cells; Bcl2 (Fig. 1C), calponin, vimentin, CD56 were positive on the spindle component while the epithelial one was intensely reactive for cytokeratin 7 and EMA (Fig. 1D).

On that ground, a biphasic SS was suspected and therefore additional immunohistochemical and molecular analyses were performed on consultation at the national referral center.

The results supported the histological diagnosis: positivity for TLE1 and negativity for PAX8 were detected and both rearrangement of the gene SYT (18q11.2) at FISH break apart analysis (Fig. 2A) and the fusion transcript SYT-SSX1 at RT-PCR analysis were confirmed. Integration of clinical-radiological, histological, immunohistochemical and molecular data led us to a final diagnosis of biphasic SS, grade 3 according to FNCLCC grading system, primitive of the thyroid gland.

Moreover histological examination of the right lobe detected an incidental papillary thyroid carcinoma (1 mm in its greater diameter) (Fig. 2B).

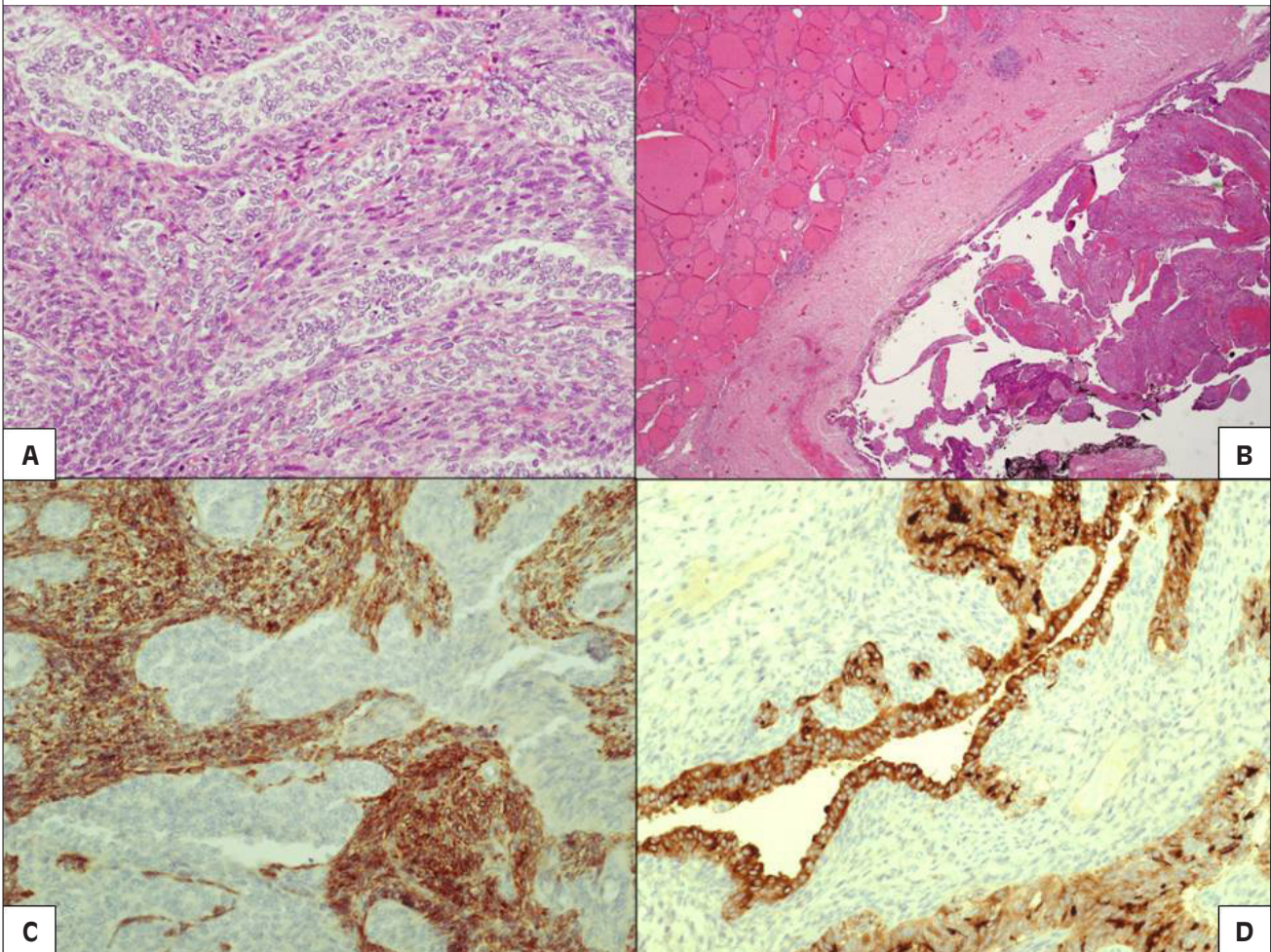
## Discussion

SS accounts for 5-10% of all soft tissue sarcomas. It usually arises in children and young adults in the extremities, especially around large joints<sup>1,2</sup>. These latter prototypical clinical aspects were missing in our case thus aggravating the patient's diagnostic evaluation.

Cases of SS localization in the thyroid, both as a primary malignancy and as a metastasis from an already documented SS, are very rare with only five described events, at the best of our knowledge<sup>3-7</sup>. In our case, the patient complained of only a cervical swelling due to a thyroid nodule without signs of thyroid dysfunction and other neoplastic lesion at total body CT-scan.

Histologically two categories of SS can be identified: biphasic and monophasic, based on the presence or absence of both epithelial and spindle cell components. Moreover areas of poor differentiation can be encountered<sup>1,2</sup>. In biphasic SS, as the one we are describing, a dual cellular population can be appreciated with both spindle cells and epithelial elements. Spindle component is characterized by small to medium cells with scant cytoplasm, ovoid nuclei with finely granular chromatin and unapparent nucleoli. The epithelial elements are usually arranged in acinar or glandular structures composed by larger cells with abundant, clear cytoplasm. Other findings we underlined in our case and which are consid-

**Fig. 1.** A: Glandular structures surrounded by highly cellular stroma with spindle cells elements (HE; 20x). B: At low magnification, a thick fibrous capsule can be appreciated separating the neoplastic proliferation from thyroid parenchyma (H&E; 2x). C: Bcl2 reactivity on the spindle cell component (SABC; 20x). D: Expression of EMA on the epithelial glandular structures (SABC; 20x).



ered usual features of SS are the presence of high mitotic count and of small, thin-walled, branching vessel with a hemangiopericytoma-like appearance. The hypothesis of SS should be confirmed throughout ancillary techniques like immunohistochemistry and molecular biology analyses: in our case the translocation  $t(X;18)(p11.2;q11.2)$  was demonstrated on histological material.

As for differential diagnoses, we had at first to rule out primary thyroid epithelial malignancies, like medullary carcinoma and undifferentiated (anaplastic) carcinoma (UTC)<sup>8-11</sup>. The first entity can be very challenging to distinguish because of its higher incidence and of its morphological variety, comprising a spindle cell component.<sup>8</sup> UTC can be characterized by spindle elements but, unlike our case, they display marked nuclear pleomorphism<sup>10-11</sup>. In our case the expression of cytokeratin by the epithelial cells only, the monomorphous morphology and the absence of marked pleomorphism of the spindle cell component helped us to exclude these entities.

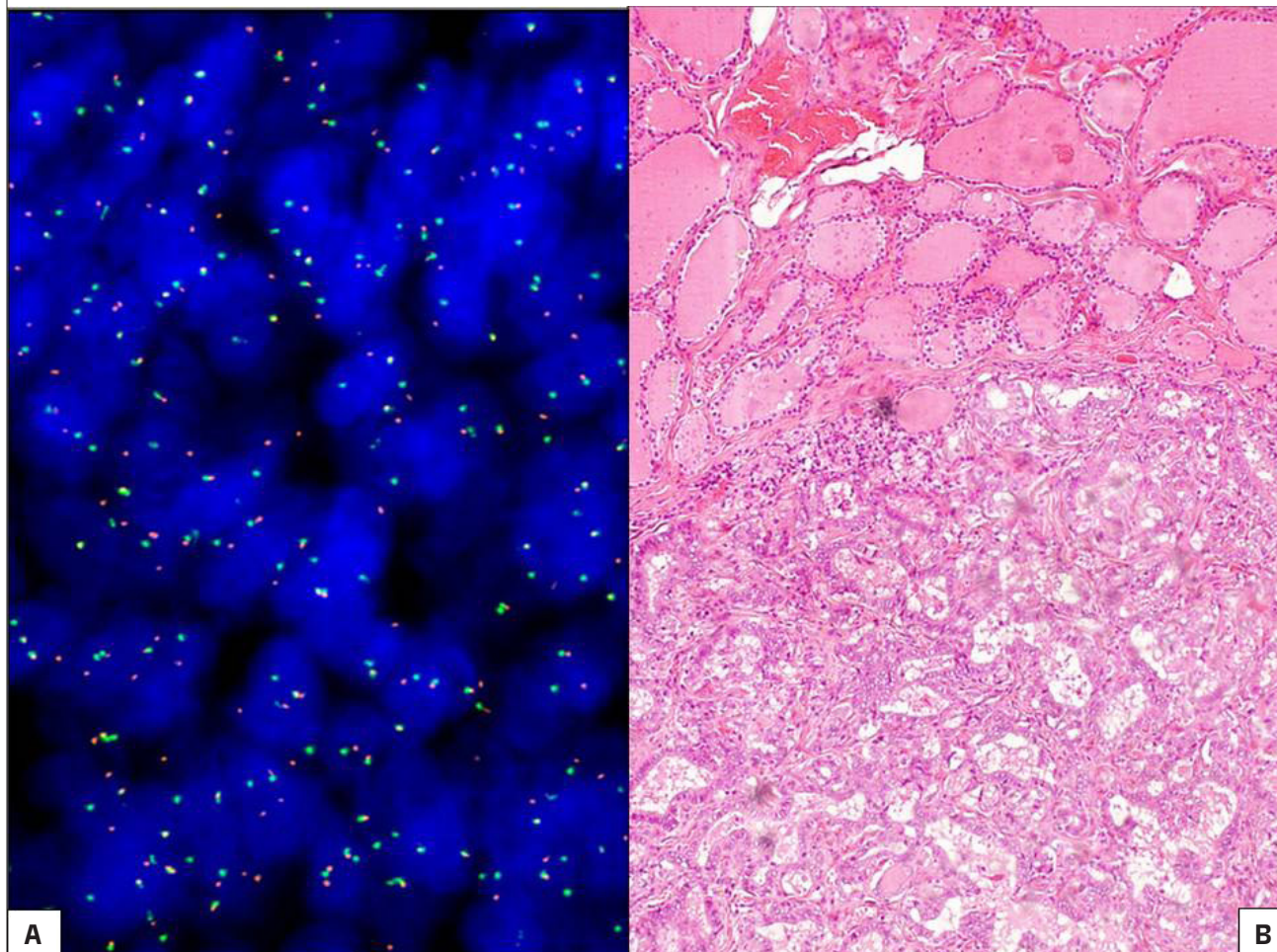
Other neoplasms that should be considered in differential diagnosis are Spindle Epithelioid Tumor with Thymus

Like Differentiation (SETTLE) and ectopic thymomas. Like SS, SETTLE is characterized by a dual cellular population (spindle and epithelial components) and with cohesive sheets of spindle cells. However it lacks the high mitotic count, which is typical of SS, and both cellular populations express cytokeratin and vimentin<sup>12-13</sup>. As for thymomas, the main challenge is to distinguish type A thymoma which usually display spindle epithelial cells with ovoid nuclei and with finely granular chromatin. Unlike SS, mitoses are infrequent. Type B thymomas can be easily ruled out since they are characterized by abundant lymphoid component and by scattered polygonal, neoplastic, epithelial cells<sup>14</sup>.

At last, other mesenchymal malignancies, both primary and metastatic, should be taken into consideration, especially sarcomas capable of epithelioid differentiation (i.e. clear cell sarcoma and epithelioid sarcoma, MPNST) and those with hemangiopericytoma-like vessels as extrapleural solitary fibrous tumor.

We considered this rare malignancy as primitive of the thyroid because it was located within the gland even if it did not infiltrate the thyroid parenchyma and was sur-

**Fig. 2.** A: FISH rearrangement pattern for SYT (SS18) gene consisting in a fusion green-orange signal corresponding to an intact copy of the gene, and split signals (separated red and green) corresponding to the rearranged alleles. B: Synchronous thyroid papillary carcinoma (H&E; 10x).



rounded by a thick fibrous capsule. Moreover, the absence of any other neoplastic lesion at different anatomic locations on clinico-radiological examination supported this hypothesis. We might speculate that primary thyroid SS may originate from pluripotential mesenchymal cell of the thyroid capsule or of thyroid stromal tissue<sup>7</sup>.

As already described, also in our case the tumor capsule was ruptured during thyroidectomy. This event seems to be related to an increased risk for local and metastatic relapses<sup>3,4</sup>. Moreover a papillary carcinoma was incidentally detected in the contralateral lobe: as far as we know, this association has never been reported before and likely to be accidental.

Finally we underline that this case is noteworthy since it describes the synchronous presence in the same organ of two completely different malignancies, the first one belonging to the soft tissue neoplasm category and the other one originating from the thyroid follicular epithelium.

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