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Original Article

A rare neurendocrine tumor of the lung: sclerosing paraganglioma. A neoplasm that is difficult to diagnose and a source of dangerous pitfalls. A case report and literature review

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Summary
An endobronchial obstructing neoformation was found in a 58-year-old man. The histology and immunohistochemical profile oriented the authors towards a diagnosis of paraganglioma, sclerosing variant. This very difficult diagnosis, especially in a pulmonary localization, may lead to erroneous conclusions both in terms of histogenetic interpretation and that of its biological behavior. The pulmonary localization of the paraganglioma is very rare and even more rare the sclerosing variant, recently reported. Differential diagnosis and literature are discussed.

Key words: paraganglioma, immunohistochemistry

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Introduction

Paraganglioma (PG) is the extra adrenal analogue of pheochromocytoma of which it repeats the structure, immunocytochemical profile and biological behavior. It is a rare neoplasm with various localizations among which the pulmonary one is very rare. The case we observed, beyond the pulmonary site, presented the histomorphological features of the very rare sclerosing variant. It is a neoplasia of very difficult diagnosis prone to dangerous pitfalls. For all these reasons, we considered it worthy of reporting.

Case – In a man of 58 years, with ischemic heart disease, bearer of a pacemaker, to a radiological control with CT Scan, the presence of a neoformation vegeto infiltrating obstructing the anterior segmental bronchus of the upper lobe of the right lung was detected (Figs. 1a,b). Bronchoscopic examination revealed the presence of a large base polypoid neoformation covered by a glossy mucosa, brownish in color almost entirely occupying the bronchial lumen (Fig. 2a). A large bioptic resection was performed on the neoformation.

After biopsy, (July 2019) and histopathologic diagnosis, the patient no longer scheduled for subsequent treatment and follow-up.

Material and methods

The biopsy specimen was fixed in formalin and embedded in paraffin. The

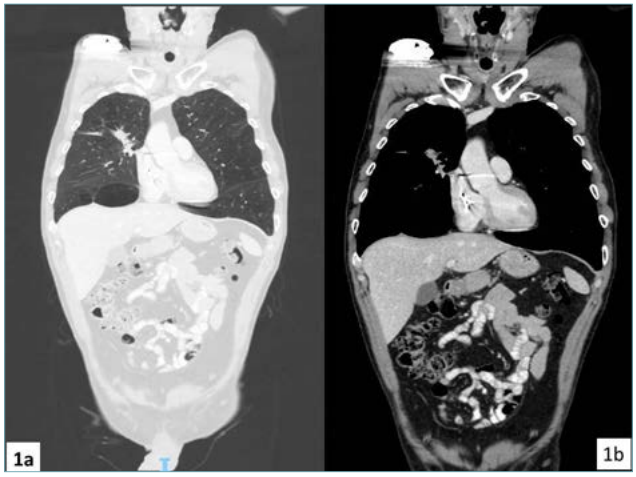

Figure 1. (a-b) Axial Total body TC scan with contrast medium. The truncation of the right upper lobar bronchus is evident.

Table I. Immunohistochemical panel.

Ab	Dilutions
Vimentin	Monoclonal 1:50
Cytokeratin MNF 116	Monoclonal 1:50
S100	Polyclonal 1:400
Chromogranin A	Monoclonal 1:100
Synaptofisin	Monoclonal 1.50
NSE	Monoclonal 1:100
CD56	Monoclonal 1:50
TTF1	Monoclonal 1:100
Ki67	Monoclonal 1:75
CD34	Monoclonal 1:20
CD31	Monoclonal 1:20
p40	Monoclonal 1:100
SMACT	Monoclonal 1:50
GFAP	Polyclonal 1:200
PD-1	Monoclonal 1:50
CD117	Polyclonal 1:400

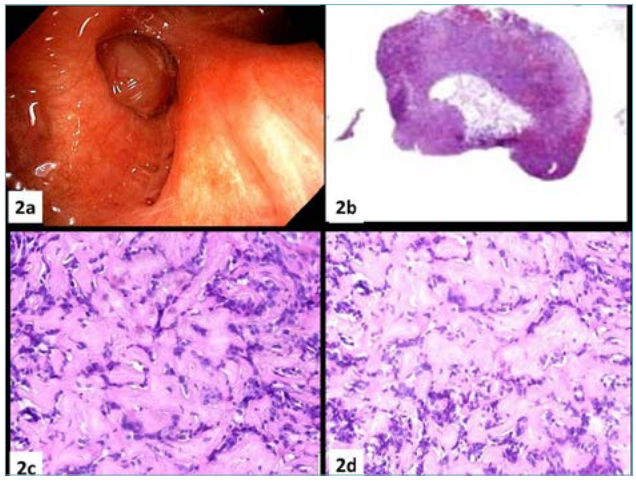

Figure 2. (a) Bronchoscopic image. Polypoid neoformation occluding the bronchial lumen; (b) Dome-shaped surgical specimen; (c-d). Subtiles cell chains compressed by exuberant desmoplasia HE 175X.

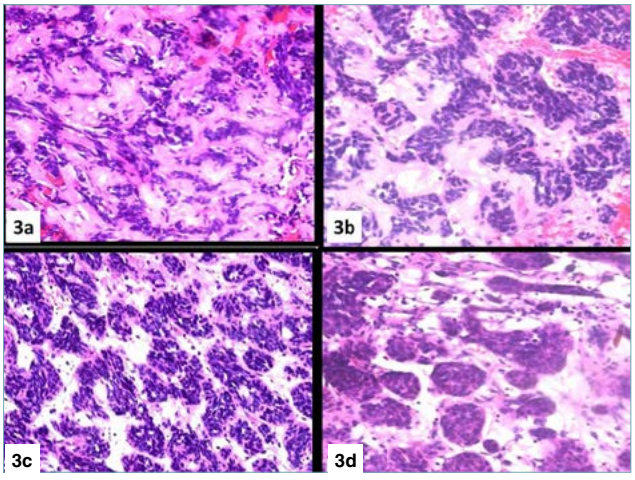

Figure 3. (a-b) Branched cellular cords surrounded by an abundant collagen matrix. HE 150, 175 X; (c-d) - *Zell Ballen*. HE 150, 175 X.

sections were stained with hematoxylin-eosin, Masson's trichrome, and Silver-impregnation according to Gomori. For immunohistochemistry a panel of antibodies was used (Tab. I).

Histology

The material under examination consisted of a grossly polypoid fragment with a maximum diameter of 4 mm (Fig. 2b). The mass was totally ulcerated. Adjacent were a few minute frustule of bronchial mucosa. The tissue was mainly made up of a proliferation of medium-sized globose elements, voluminous roundish hyperchromatic nucleus, mainly arranged in chains (Figs. 2c,d) or joined to form thin branched cords compressed and separated by a dense and abundant fibrous matrix (Figs. 3a,b). In the periphery, where the fibrous tissue was more lax and less abundant, elements aggregated into nodular formations type *Zell Ballen* (Figs. 3c,d). Silver stainig according to Gomori allows recognition, although distorted, the characteristic alveolar pattern of the PG (Figs. 4a), while Masson's trichrome confirmed the intense desmoplasia (Figs. 4b). Mitotic activity was practically absent.

The results of the immunohistochemical investigation are shown in Table II.
On the basis of morphological data and the results of immunohistochemical investigation, after having examined a vast differential diagnosis panel,a diagnosis of primary broncho-pulmonary paraganglioma, sclerosing variant was favored.

Discussion

The adrenal medulla and the extra adrenal paraganglia, having the same embryological origin, the same histological structure and the same function constitute the adrenal sympathetic neuroendocrine system. The extra adrenal paraganila are structures distributed along the paraortico-praventebral axis, in parallel with the distribution of the sympathetic nervous system. They produce neurotransmitters (epinephrine and norepinephrine) that activate the interneuronal synapses of the sympathetic system. The paraganglias with respect to the site are divided into branchiomeric,intravagal, aortosympatetic and visceral. The common origin from the Neural crest with the cells of the diffuse neuroendocrine system explains the common dyeing, histochemical, immunohistochemical and ultrastructural affinity, making it, especially in lung localizations, very difficult for diagnostic differentiation [1].
Pulmonary localization of PG is among the rarest. In a collection of 152 cases, the pulmonary site appears only in 3 (2%) [2]. A review of the literature in 1995 reported 25 cases up to that date [3]. Subsequent to that time another 13 have been reported In the literature in the English language [3-14].
The differential diagnosis of this lesion in the lung with more frequent carcinoid tumors is not always easy and lies in subtle morphological differences and immunophenotypic expressiveness. So much so that according to some AA, while not excluding the possibility of their existence in such a location, it is very difficult to determine their actual frequency given the difficulty differential diagnosis with carcinoid [1]. On the morphological level differential diagnosis can be fairly easy in the case of lesions in the classical form. It becomes very difficult if not impossible in the atypical or undifferentiated forms or in the case of not uncommon variants.
On the basis of immunophenotypic differentiation it is a little less arduous as can be seen from Table III.
Although previous cases of PG with marked sclerosis phenomena have been reported, a specific sclerosing variant was defined in 2006 [15]. In that publication, the result of a multcentric study conducted at four large North American institutions, 16 cases were collected and described. Subsequent to this first publication, five other individual cases followed, one of which was bronchopulmonary [16-20].
The morphological patterns presented in these publications are completely superimposable to the one observed to us. Our differential diagnostic procedure followed the same scheme proposed in these articles. In view of the lack of the classic PG structure, the infiltrative aspect of the lesion, one can consider the possibility of a primitive or secondary pulmonary malignancy, and among these those with desmoplasty. Secondly, the neuroendocrine expression introduces a discussion between the possible nuroendocrine lesions of the lung. The morphological picture as a whole does not integrate the typical aspects of any of the nuroendocrine neoplasms of the lung. In addition, in the peripheral areas, less affected by desmoplasia, the characteristic *Zell Ballen* of the PG are easily recognizable (Figs. 3c-

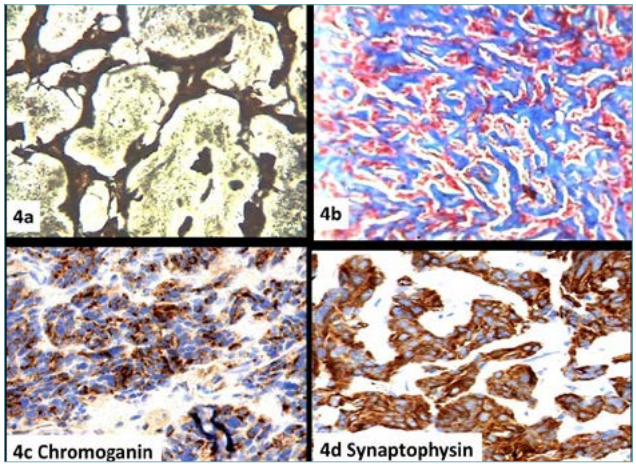

Figure 4. (a) Silver staining - Despite the thickening of the septa, the characteristic alveolar structure of the PG is still recognizable 150, 250 X; (b) Masson Trichrome intense desmoplasia 175 X; (c) Chromogranin; (d) Synaptophysin - 200X.

Table II. Immunohistochemistry results.

Ab	Vim	Ck	S100	Chromogr	Synapto	NSE	CD56	TTF1	Ki67	CD34	CD31	P40	SMACT	GFAP	PD-1	CD117
	+*	-	+*	+	+	+	+/-	-	low	-	-	-	-	-	-	-
Fig.	5d		5c	4c	4d	5a	5b									

**sustentacular cells.*

Table III. PG vs carcinoid immunohistochemistry.

Ab	Parganglioma	CARCINOID
CK	.	+
SYNAPTO	+	+
CHROMOGR	+	+
NSE	+	+
TTF1	-	+
S100	+*	-

**sustentacular cells.*

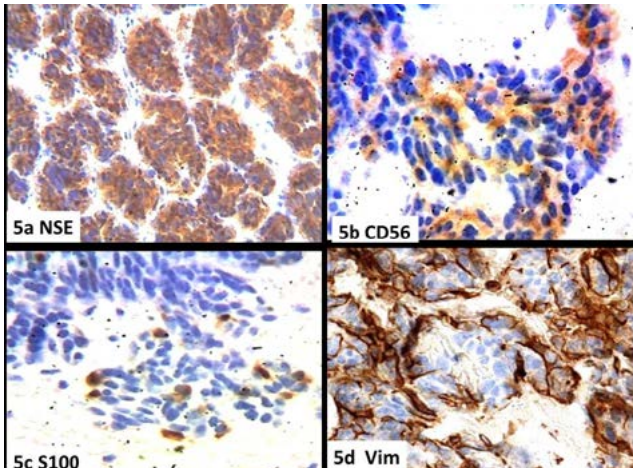

Figure 5. (a) NSE; (b) CD56; (c) S100 (sustentacular cells) 150X; (d) Vimentin 200X.

d). In addition, the silver stainig highlights, albeit distorted, the characteristic alveolar pattern (Fig. 4a).

On the imunohistochemical level, despite the clearly positive neurendocrine markers (Figs. 4c,d, 5a,b), the negativity for cytokeratins and TTF1 makes a neoplasm of the carcinoid family unlikely. Even if scattered, because of sclerosis, but still placed on the periphery of the cellular cords, positive S100 cells are present interpretable as *sustentacolar* (Fig. 5c). Vimentin has an arrangement similar to that of the argyrophilic fibers that surround the alveolar spaces. The low proliferation index and the absence of mitotic figures suggest that the lesion is low in aggressiveness. The incomplete removal, if not followed by a radicalizing intervention, could cause recurrence.

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Case Report

Solitary fibrous tumor of the orbital region: report of a case with emphasis on the diagnostic utility of STAT-6

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Summary

Solitary fibrous tumor (SFT) is a relatively rare soft tissue neoplasm originally described in the pleura. Since its first description, several cases arising in extra-pleural superficial and deep soft tissues have been reported in the literature. SFT arising in the head and neck region is quite rare, representing about the 6% of all SFTs, and the sinonasal tract is the most common involved region, followed by the orbit, the oral cavity and the salivary glands. Herein, we report the clinico-pathologic features of a rare case of SFT of the orbital region, emphasizing the diagnostic role of the immunomarker STAT-6. A 52-year-old female presented to our hospital with a nodular mass in the left orbital region. Histological examination revealed a uniformly hypercellular tumor composed of pale to slightly eosinophilic bland-looking spindle cells arranged in intersecting short fascicles with interspersed stellate-shaped, keloid-type collagen fibers. Notable hypocellular areas, perivascular hyalinization and hemangiopericytoma-like branching vascular pattern were absent. Immunohistochemically, neoplastic cells were diffusely positive for vimentin, CD34 and STAT-6. The introduction of STAT-6 in daily diagnostic practice is helpful to confidentially render a diagnosis of SFT even in the presence of unusual morphology and site.

Key words: solitary fibrous tumor, soft tissue tumor, spindle cell lesion, orbit, STAT-6

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Introduction

Solitary fibrous tumor (SFT) is a relatively rare soft tissue neoplasm originally described in the pleura [1]. Since its first description, several cases arising in extra-pleural superficial and deep soft tissues have been reported in literature [2-4]. SFT may also arise in visceral sites, including kidney, mammary gland, liver, pancreas and gastrointestinal tract [5-10]. SFTs of the head and neck region are relatively uncommon, and the orbit is the second most common site (25% of cases) after the sinonasal tract (30% of cases) [11]. More rarely the tumor may occur in the oral cavity (15% of cases) or salivary glands (14% of cases) [11]. Orbital SFT usually arises as a unilateral progressive slow-growing tumor, clinically detectable for the onset of proptosis, eyelid swelling or palpable mass [12-14]. Other symptoms, such as visual deficit and ptosis, depend on the size and exact location of the neoplasm [14]. The most common histological features of classic pleural and extra-pleural SFT are: i) bland-looking spindle to ovoidal cells arranged in a "patternless" growth pattern; ii) rich vascular component composed by small- to medium-sized branching vessels, often with perivascular hyalinization and hemangiopericytoma-like pattern;