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

Giovanni Africa¹, Francesca M. Plutino¹, Marcello Filotico²

¹ Grande Ospedale Metropolitano “Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; ² Fondazione Cad. Panico, Tricase, LE, Italy

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

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
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 Bal len (Figs. 3c,d). Silver staining 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.

**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 |
| Synaptophysin | 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 |
| S100 | Monoclonal 1:400 |
| SMACT | Monoclonal 1:50 |
| GFAP | Polyclonal 1:200 |
| PD-1 | Monoclonal 1:50 |
| CD117 | Polyclonal 1:400 |

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

**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 Bal len. HE 150, 175 X.
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 paraganglia 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.

Pulmonary localization of PG is among the rarest. In a collection of 152 cases, the pulmonary site appears only in 3 (2%) cases. A review of the literature in 1995 reported 25 cases up to that date. Subsequent to that time another 13 have been reported in the literature in the English language.

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 of differential diagnosis with carcinoid. 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.

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 desmoplasia. Secondly, the neuroendocrine expression introduces a discussion between the possible neuroendocrine lesions of the lung. The morphological picture as a whole does not integrate the typical aspects of any of the neuroendocrine 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-4d).

Table II. Immunohistochemistry results.

| Ab | Vlm | 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.
d). In addition, the silver staining highlights, albeit distorted, the characteristic alveolar pattern (Fig. 4a). On the immunohistochemical level, despite the clearly positive neuropeptide 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 sustentacular (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.

References
1 Tumors of Adrenal Glands and Extraadrenal Paraganglia. AFIP Atlas of Tumor Pathology, Series 4. Washington DC: ARP 2007, p. 283.
2 Feng N, Zhang WY, Wu XT. Clinicopathological analysis of paraganglioma with literature review. World J Gastroenterol 2009;15:3003-8. https://doi.org/10.3748/wjg.15.3003
3 Skodt V, Jacobsen GK, Helsted M. Primary paraganglioma of the lung: report of two cases and review of literature. APMIS 1995;103:597-603. https://doi.org/10.1111/j.1699-0463.1995.tb01412.x
4 Hironaka M, Fukayama M, Takayashiki N, et al. Pulmonary gangliocytic paraganglioma: case report and comparative immunohistochemical study of related neuroendocrine neoplasms. Am J Surg Pathol 2001;25:688-93. https://doi.org/10.1097/00000478-200109000-00020
5 da Silva RA, Gross JL, Haddad FJ, et al. Pulmonary paraganglioma: case report and literature review. Clinics (Sao Paulo) 2008;63:89-6. https://doi.org/10.1590/s1807-59222006000100015
6 Kim KN, Lee KN, Roh MS, Choi PJ, et al. Pulmonary paraganglioma manifesting as an endobronchial mass. Korean J Radiol 2008;9:87-90. https://doi.org/10.3348/kjr.2008.9.1.87
7 Ceberut K, Müselehiddinoglu A, Akar I, et al. Primary pulmonary paraganglioma: a case report. Turk Jem 2010;14:14-6.
8 Huwer H, Kalweit G, Schläfer H, et al. Pulmonary paraganglioma: case report and literature review. Pneumologie 2011;65:742-4. https://doi.org/10.1055/s-0031-1286635
9 Zhang JJ, Liu T, Peng F. Primary paraganglioma of the lung: a case report and literature review. J Int Med Res 2012;40:1617-26. https://doi.org/10.1177/0003489412464617
10 Ibraheema T, ElGhazaly H, Madkoura A, et al. Primary paraganglioma of the lung: a case report. Egyptian Journal of Bronchology 2014 8:64-5.
11 Huang X, Liang QL, Jiang Let al. Primary pulmonary paraganglioma: a case report and literature review. J Med Case Rep 2015;9:166. https://doi.org/10.1186/s13256-015-0639-z
12 Chan J, Sangani R, Oduntan O, et al. Primary Pulmonary paraganglioma presenting as a solitary lung nodule. 150#4S Chest october 2016.
13 Muriana P, Bandiera A, Ciriaco Pet al. A case of endobronchial paraganglioma. Ann R Coll Surg Engl 2017;99:e28-e30. https://doi.org/10.1308/rcssann.2016.0284
14 Plaza JA, Wakely PE Jr, Moran Cet al. Sclerosing paraganglioma: a case report and review of literature. Medicine 2015;94:e1271. https://doi.org/10.1097/MD.00000000000001271
15 Fiorentino G, Annunziata A, De Rosa N, Primary paraganglioma of the lung: a case report. J Med Case Rep 2015;9:166. https://doi.org/10.1186/s13256-015-0639-z
16 Evankovich J, Dedhia RC, Bastaki JM, et al. Primary sclerosing paraganglioma of the thyroid gland: a case report. Ann Otol Rhinol Laryngol 2012;121:510-5. https://doi.org/10.1177/000348941212100803
17 Santi R, Franchi A, Saladino V, et al. Sclerosing paraganglioma of the carotid body: a potential pitfall of malignancy. Head Neck Pathol 2015;9:300-4. https://doi.org/10.1007/s12105-014-0569-x
18 Ng E, Duncan G, Choong AM, et al. Sclerosing parangangliomas of the carotid body: a series of a rare variant and review of the literature. Ann Vasc Surg 2015(7):1454.e5-1454.e12. https://doi.org/10.1016/j.avsg.2015.04.083
19 Blefaria NDA, Ellezera DD, Vilaire RE, et al. Sclerosing paranganglioma of the carotid body in a child: A diagnostic and therapeutic challenge. International Journal of Pediatric Otorhinolaryngology Case Reports 2019;23:100663. https://doi.org/10.1016/j.ipedo.2019.100663

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.