



## Clinical-Evolutive and Morphopathological Particularities in Primary Teratocarcinoma of Anterior Mediastinum in Adolescents Clinical Case Presentation and Literature Review

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### Abstract

*Extragonadal germ cell tumors are rare in children, being diagnosed starting with the neonatal period and in adolescents, the anterior mediastinum being the most common location involved in the neoplastic process. The term "teratocarcinoma", according to WHO terminology, is used in cases of the combination of teratoma with embryonic carcinoma. The authors present the analysis of the clinical evolution, the results of laboratory and imaging investigations, compared with the data of the histopathological examination of an adolescent with a massive tumor formation of the anterior mediastinum with extension in the left hemithorax. The authors conclude that teratocarcinoma of the anterior mediastinum is characterized by an extremely aggressive behavior, which in a short period of time can reach giant dimensions and advanced stages of the disease, imposing the need for a greater degree of suspicion in the diagnosis of these tumors. Despite the complete ablation of the tumor, the risk of developing metastases in the intrathoracic organs, found postoperatively, which are not always detected preoperatively, persists. Extensive histological examination of the excised specimen is very valuable in assessing the share of immature tissues and malignant germ components, in the case presented a large amount of embryonic carcinoma was identified, which, along with immature teratomatous components, probably determined the aggressive evolution of the neoplasm.*

### Introduction

Extragonadal germ cell tumors are a heterogeneous group of rare benign and malignant neoplasms, which develop due to stopped migration of primordial pluripotent germ cells in the early embryonic period, comprising the full range of histopathological subtypes of these neoplasms found in gonads<sup>[1]</sup>, including: teratoma (mature and immature), seminoma, embryonic carcinoma, choriocarcinoma and combined germ cell tumors, each histological type being present isolated or associated with another component,

creating mixed tumors<sup>[2]</sup>. Mediastinal germ cell tumors in children and adolescents constitute about 3-7% of all these tumors characteristic of this age and 6-25% of mediastinal tumors, in 85% of cases mature teratomas are found, located predominantly (80% of cases) in the anterior mediastinum<sup>[3]</sup>.

Classically, germ cell tumors fall into two categories, including seminomas (dysgerminomas) and nonseminomatous germ cell tumors, which include teratoma (benign or immature), embryonal carcinoma, yolk sac tumors, choriocarcinoma, and

mixed tumors<sup>[2]</sup>. Of interest is the classification proposed by Kalhor N.<sup>[4]</sup>, according to which mediastinal germ cell tumors are divided into:

1. teratoma

- Mature
- Immature
- With malignant component:

- Type I - with another germ cell tumor (seminoma, yolk sac tumor, carcinomembryonic, choriocarcinoma);
- Type II - with an epithelial malignant tumor (adenocarcinoma, squamous cell carcinoma, etc.)
- Type III - with a mesenchymal malignant component (rhabdomyosarcoma, angiosarcoma, etc.)
- Type IV - any combination of previous types

2. seminoma

3. Embryonic carcinoma

4. Choriocarcinoma

5. Combined germ cell tumor - a combination of any of the above tumors without teratomatous elements.

The authors are of the opinion that if teratomatous elements are present, then these tumors should be classified into different types of teratomas<sup>[4]</sup>.

Mixed germ cell tumors are a combination of the elements of different germ tumors, more often being found the association between immature teratoma with embryonic carcinoma and yolk sac tumor<sup>[5]</sup>. Chetaille B., and coauthor. (2010) indicate that mixed germ cell tumors include seminomas in association with components of nonseminomatous germ cell tumors, an idea confirmed in other papers.

Along with the histological classification, the staging of these tumors has also been proposed, although this can often be impossible. According to the staging system proposed by Kalhor N., Moran C.A. (2018) we distinguish:

Stage I - limited thorax at the level of the mediastinal compartment without invasion in adjacent organelles such as the pleura or pericardium;∞

Stage II - tumors show macro- and microscopic invasion in adjacent structures, such as the pleura, pericardium and large vessels;

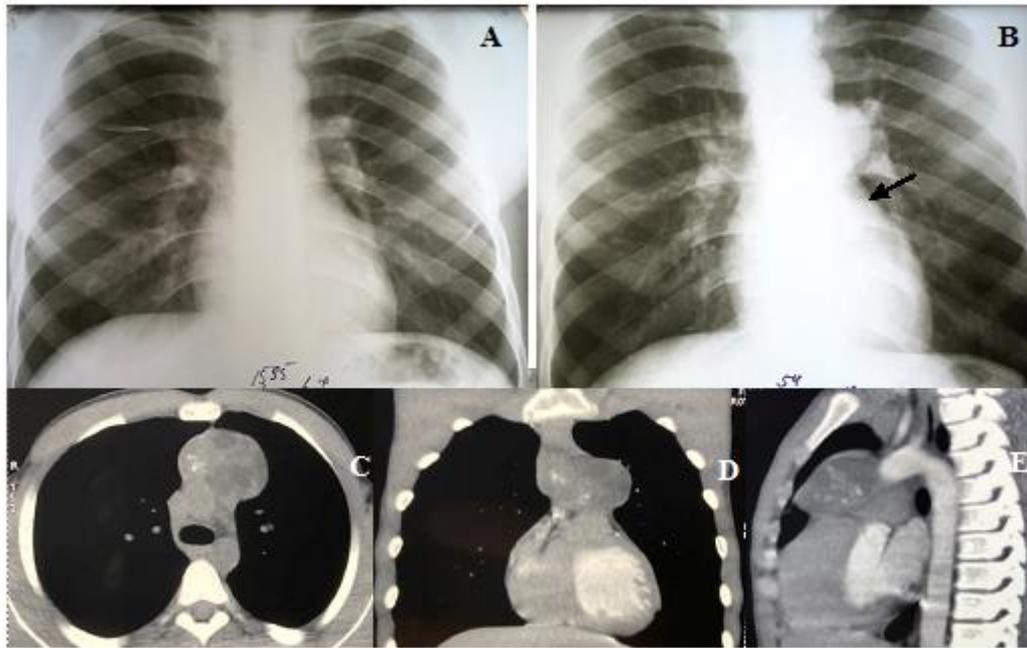
Stage III - metastatic disease;

- IIIA - metastases in the intrathoracic organs (lymph nodes, lungs, etc.)
- IIIB - extra-thoracic metastases;

The mediastinal teratom is a special type of tumor that comes from one or more of the three embryonic layers of primordial germ cells (ectoderm, mesoderm and endoderm), depending on the histomorphological features being classified into mature, immature and teratoma with malignant component<sup>[4,6]</sup>. At the same time, the literature describes the notion of "malignant teratoma", which includes three types, including: immature teratoma, teratoma with other malignant tumor components of germ cells (such as yolk sac tumor, embryonal carcinoma, choriocarcinoma and seminoma) and malignant transformation teratoma, which involves a malignant tumor with non-germ cells that occurs in a pre-existing mature teratom<sup>[7]</sup>. The term "teratocarcinoma" is also found in the literature<sup>[8,9]</sup>, which, according to WHO terminology, is used in cases with the combination of teratoma with embryonic carcinoma<sup>[10,11]</sup>.

### Case Report

A 15-year-old adolescent presented to National Scientific-Practical Center for Pediatric Surgery "Natalia Gheorghiu" with a history of dyspnea due to physical exertion and chest pain for a period of approximately 6 months. The patient is from an outbreak of tuberculosis, which is why he is on the record of the phthisiopneumologist. At the radiological examination previously performed, data of intrathoracic tumor formations were not determined (Fig. 1A). In January 2020, taking into account the patient's accusations, the family doctor indicated a chest radiograph, where a volume formation of the anterior mediastinum was found (fig. 1B), later confirmed at CT (fig. 1C, D, E).

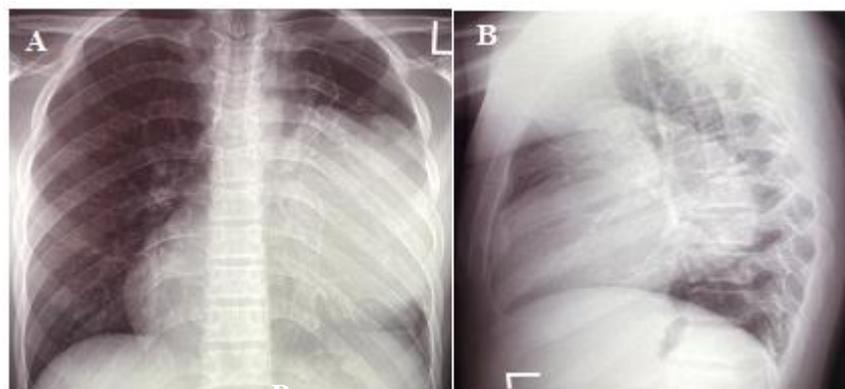


**Fig. 1.** Patient S.I., y/b 2005. A - chest radiograph performed on 13.08.2018; B - chest radiograph performed on 15.01.2020; C, D, E - CT performed on 06.02.2020 where an inhomogeneous tumor formation of the anterior mediastinum is appreciated (explanations in the text)

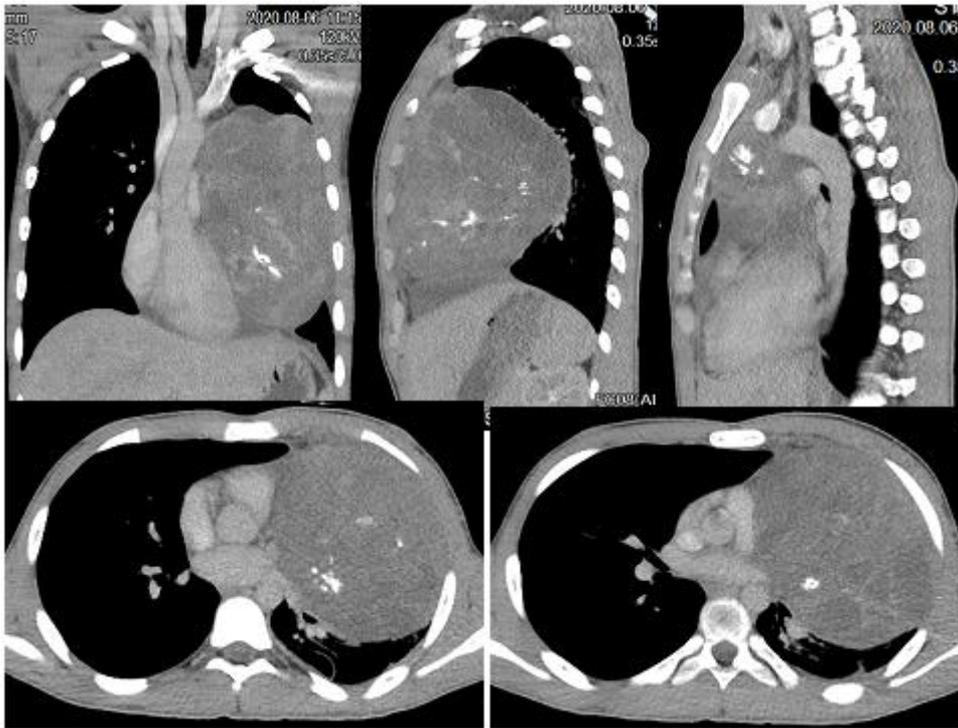
The patient disappeared from the attention of doctors for a period of 7 months in connection with the pandemic. On 05.08.2020 the patient was hospitalized in National Scientific-Practical Center for Pediatric Surgery "Natalia Gheorghiu" with the same accusations. At the time of admission, examination of the chest revealed bulging of the left thoracic wall with reduced respiratory movements.

On radiological examination performed on the day of hospitalization revealed the presence of a large intrathoracic volume formation on the left (Fig. 2A, B). On CT, a hypodense formation was found,

with a multicomponent inhomogeneous appearance - mainly multilocular cystic, with suspicious necrosis areas and multiple intrastromal calcinates, polylobulated, clearly delimited, of massive dimensions (17.4 x 13.3 x 11.0 cm), originating in the left anterior mediastinum extending into the left hemithorax, with significant compression and posterior displacement of the left main bronchus and pulmonary trunk; signs of minimal pericardial effusion; minimal pleurisy on the left. Compared to the CT from 06.02.2020, an obviously negative evolution was found (fig. 3)



**Fig. 2.** Patient S. Preoperative chest radiography: the presence of a giant formation located in the left hemithorax with contralateral displacement of the mediastinum. Explanations in the text.



**Fig. 3.** Patient S. Preoperative CT scan (explanations in text)

Ultrasound of the internal and testicular organs did not show any pathology. Routine laboratory blood tests and urine tests were approximately within normal limits except for the presence of anemia (Hb - 90.00 g / l; E -  $3.00 \times 10^6$  / uL), leukocytosis ( $L-13.80 \times 10^9$  / L), lymphopenia ( $l - 12.00\%$ ), increase in ESR values (55.00 mm / h) and fibrinogen (5.68 g / l). Serum lactate dehydrogenase values were 175.00 U / L.

After a preoperative preparation, the patient underwent surgery, performing a left latero-posterior thoracotomy in the intercostal space IV. Intraoperatively, in the left hemithorax, anterior to the pulmonary hilum, a giant tumor formation was found, of hard-elastic consistency, pearly color with a purple hue, which adheres to the anterior thoracic wall, to the pericardium and posterior to the lung tissue. Using the element of electrocoagulation and coagulation with argon plasma, we resorted to mobilizing the formation from adjacent tissues, noting that its origin was in the anterior mediastinum, we found a clear demarcation of tumor adhesion to the wall of the main vessels. Complete ablation of the tumor was performed without any damage to the vital structures with resection of the lung sector

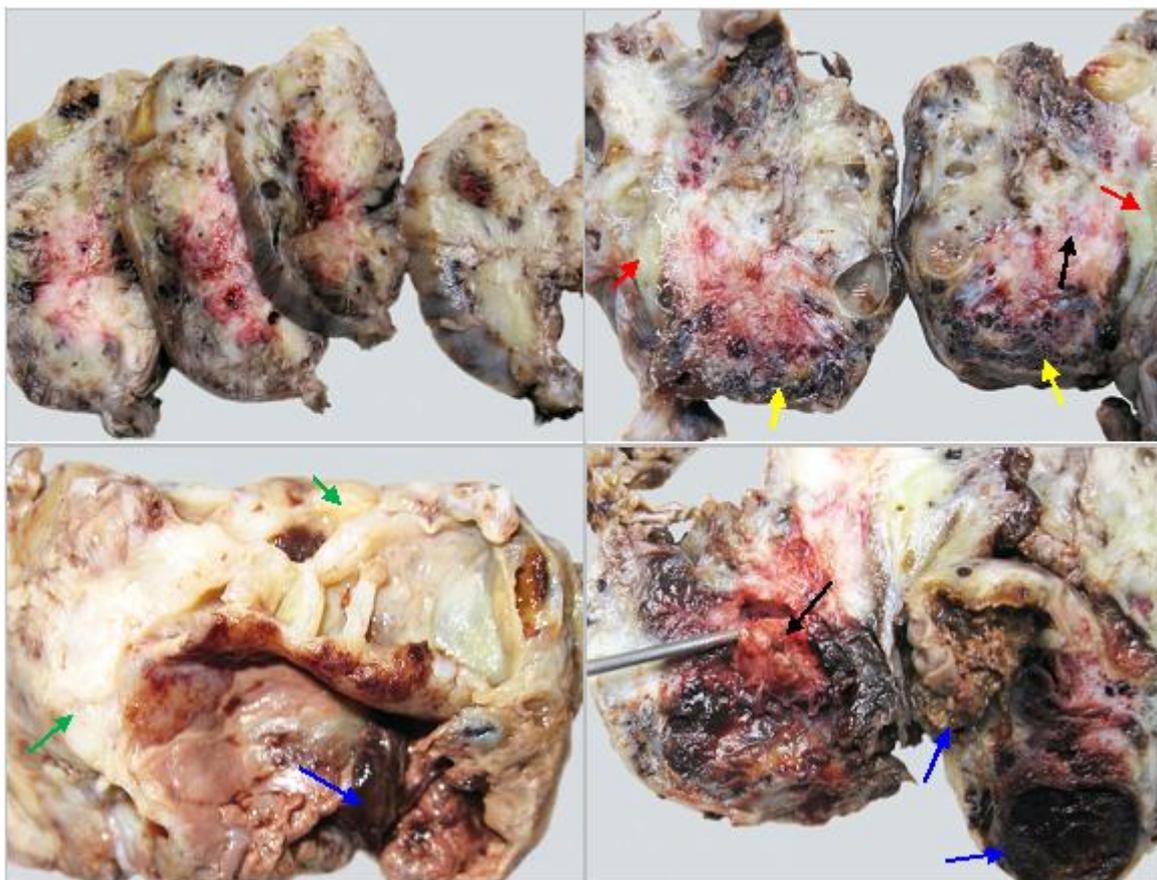
attached to the tumor. The pleural cavity was drained with a tube by microthoracotomy in the intercostal space VI. The operation ended with the restoration of the anatomical plane in layers. The postoperative period evolved without complications with the restoration of the patient's satisfactory condition. Pleural drainage was removed after 72 hours with radiological control (Fig. 4).



**Fig. 4.** Patient S. Chest X-ray performed on the 3rd postoperative day - some formations in the right lung are not observed, on the left - condition after removal of the tumor

Histological investigations revealed a capsule up to 0.3 cm thick unevenly differentiated from tumor tissue, the latter presenting a solid mass with cystic structures, which had a chaotic fibrillar focal architecture of dense and fleshy consistency, with liquefaction aspects pseudogelatinous yellowish tinge, among which are attested undifferentiated tissue spaces or similar to brain tissue with necrotic aspects and cystic structures with dimensions of 0.2-0.5 cm. Along with them, cysts with dimensions of 3-4 cm in diameter with clear serous or yellowish content were also observed. Brown congestive spongy areas have

been documented in some peripheral areas. Some cystic structures had a cavernous appearance with the content of "coffee grounds" or granular surfaces with the appearance of brown deposits. Simultaneously with cartilaginous islets, the presence of osteocartilaginous structures was observed, which mimicked the dental appearance. Along with these, a varicose dispersed congestive vascular component was determined with the presence of thrombi. Unique small cysts with sebum content were present in the denser fibrillar areas.



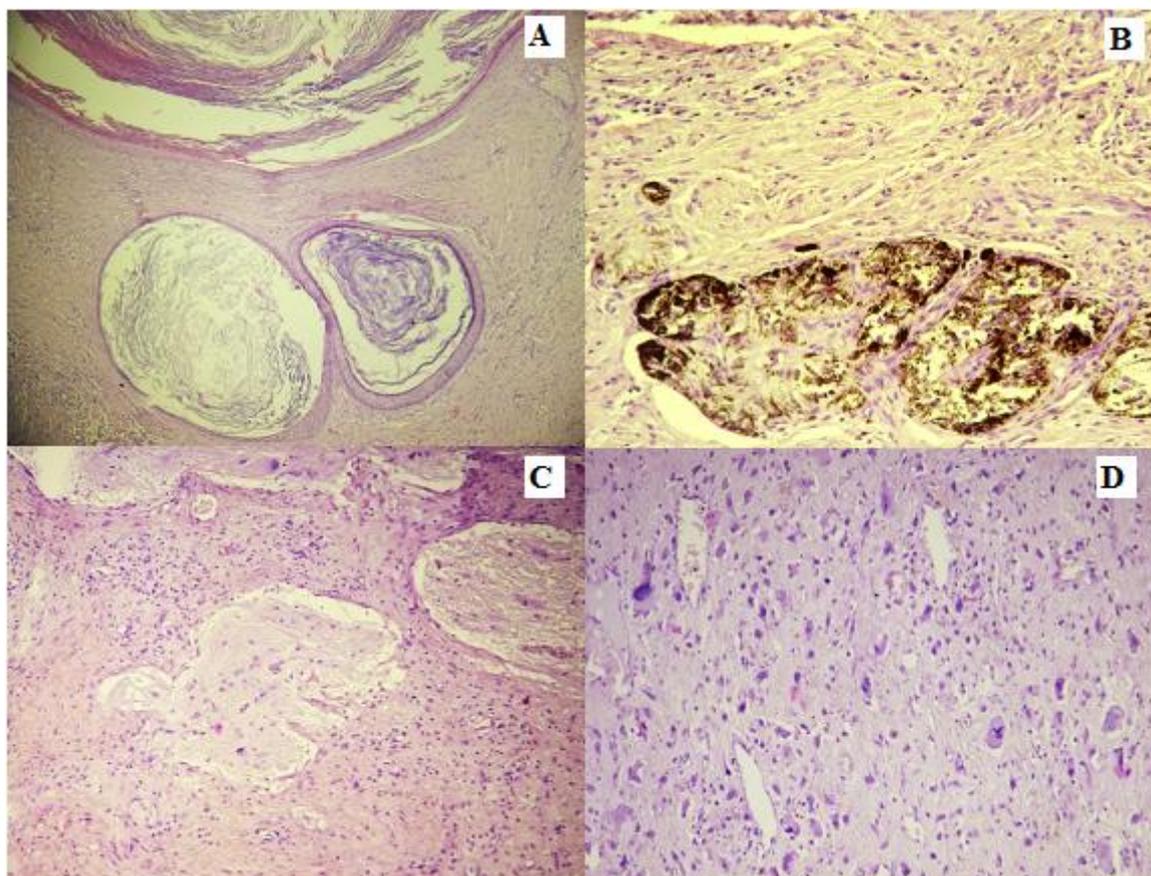
**Fig. 5.** Macroscopic appearance of the resected neoplasm sectioned in series, characterized by a solid and cystic tissue component with aspects of pseudomixomatous focal liquefaction (red arrow), undifferentiated homogeneous structures (green arrow), spongy areas (yellow arrow of cartilage) and insular cartilage in the form of a solitary cone (black arrow), granular surfaces with brown deposit aspects (blue arrow), varicose vascular structures with blood, thrombi.

Histological examination revealed a mixed fibrillar-cystic and cellular architecture, with components of ecto-, meso- and endodermal origin with mature and immature morphological

features associated with malignant germinal elements with proliferative and / or mitotic activity.

Tissues of ectodermal origin, which accounted for about 15-20% of the tumor volume, were located in plateaus and scattered foci, with predominant nerve tissue, including nerve fascicular fibers and brain nerve tissue. At the same time, sebaceous structures followed by keratin, mature and immature epidermal cysts could be observed.

Transitional epithelium, melanocyte-melanophore islets with an abundance of melanocyte pigment (fig. 6). Nerve tissues were characterized by a glial-astrocytic dysmorphia, giant neuronal-ganglionic aspects, sometimes being found unique mitosis, neurodegenerative changes, scattered hemosiderophagy.

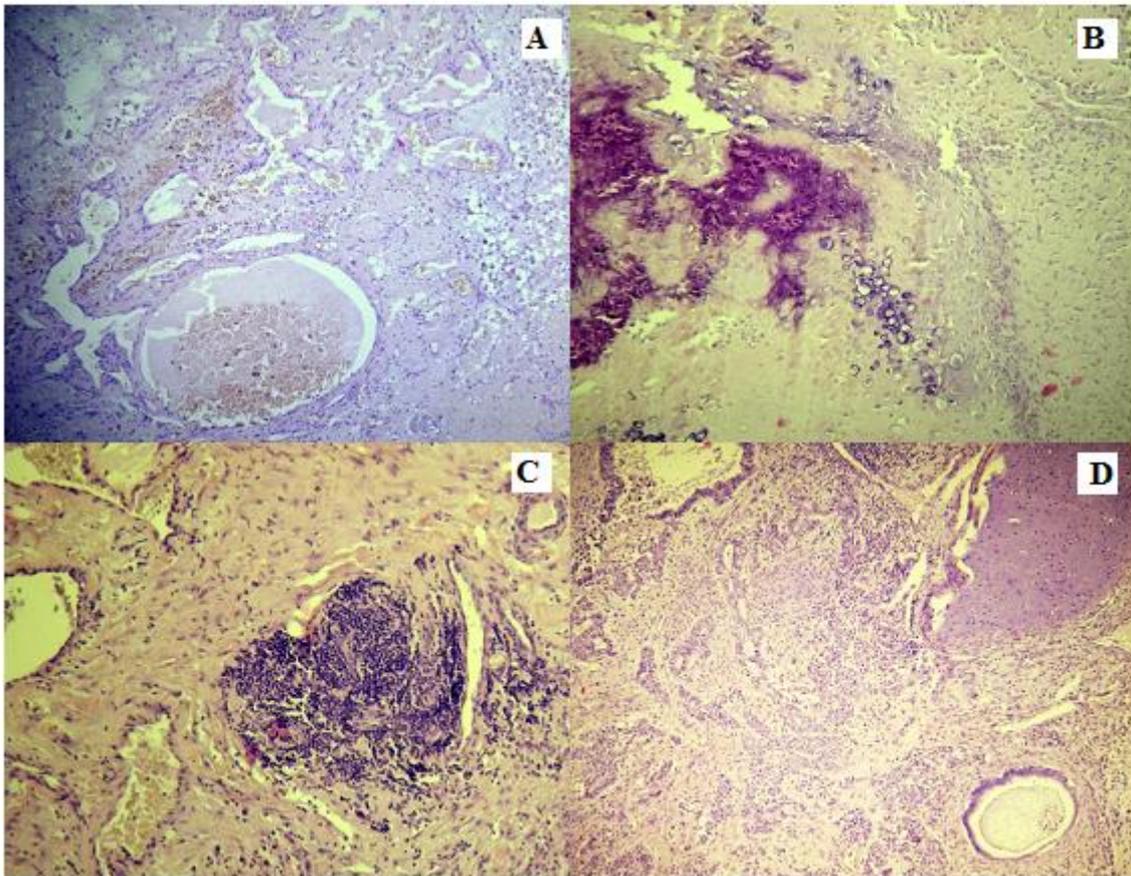


**Fig. 6.** Tissue section of the excised specimen that demonstrates histological aspects of the component of ectodermal origin: A - epidermal cysts and sebaceous glands in spaces of mature connective-muscular fibrillar tissue; B - melanocyte-melanophore cell structures with abundance of pigment; C-D - nerve tissues with cellular dysmorphia, malignant glial-astrocytic and giant-cellular aspects with hyperchromic dysplastic nuclei and mitotic activity, neurodegenerative changes.

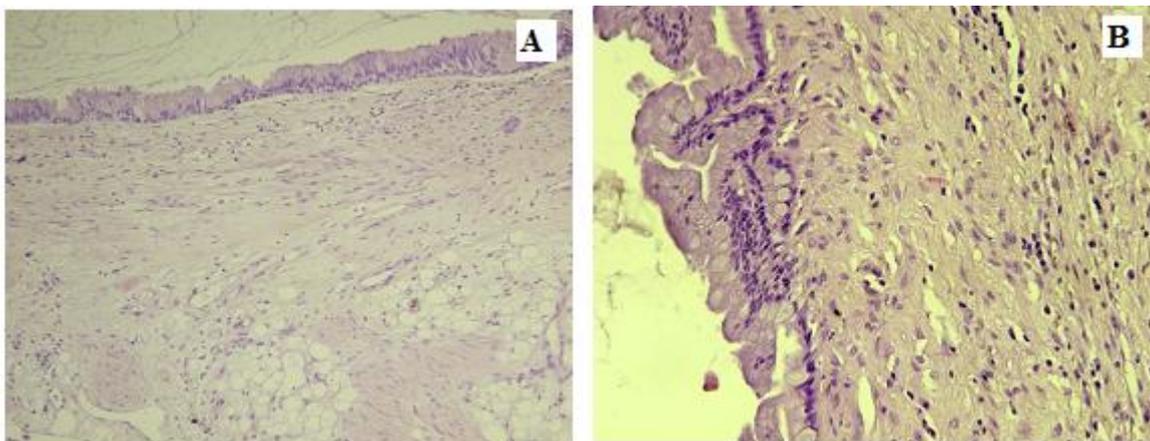
Derivatives of mesodermal origin (25% - 40%) were represented by structures with varying degrees of differentiation, including dysplastic vascular elements with cavernous-cystic and angiomatous appearance, fusiform cellular fibrillar tissue of varying density, focal fibrocollagenized connective tissues and muscle elements. skeletal and smooth, cellulo-adipose tissues, cartilage and osteo-cartilaginous structures with varying degrees of maturation,

pseudomixomatous and pseudonodular and pseudofollicular lymphatic tissues, including in aspects of dispersed lymphocytes, hematopoietic elements (Fig. 7).

The endodermal component (5-9%) was represented by glands, cysts with respiratory and gastrointestinal epithelium, undifferentiated tubulo-alveolar cellular structures and tissue-cellular masses (fig. 8).



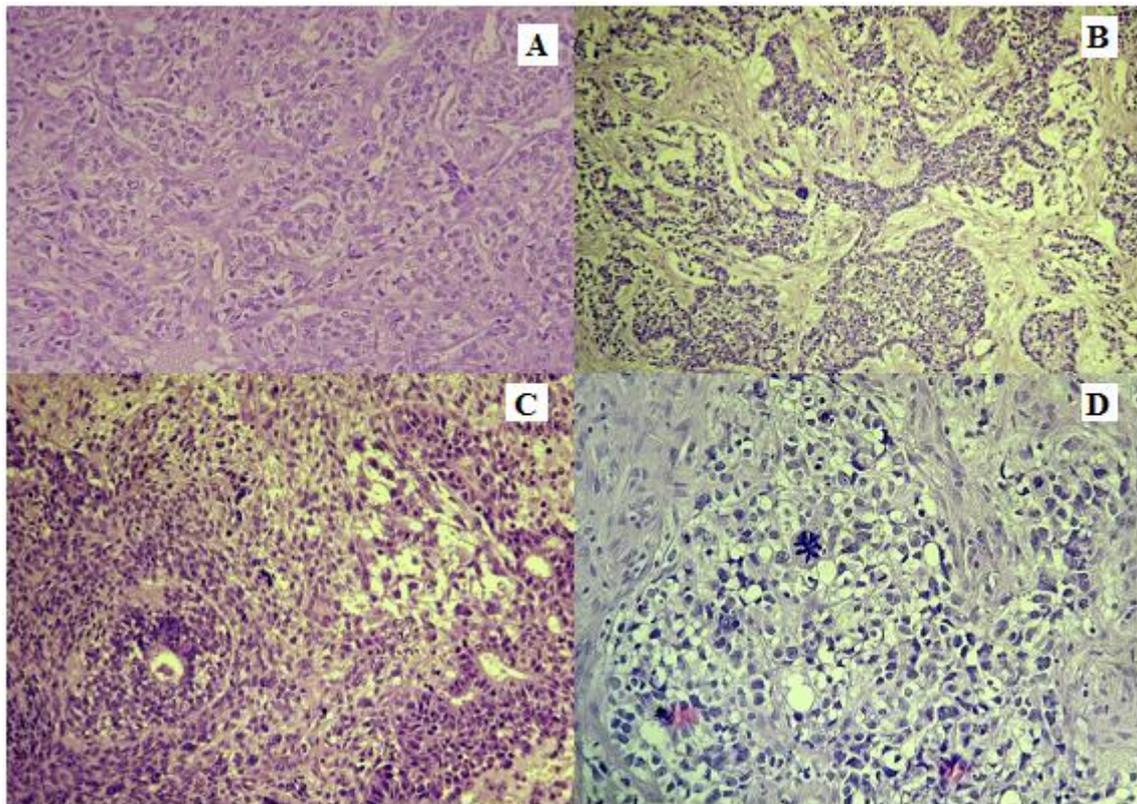
**Fig. 7.** Tissue section of the excised specimen that demonstrates histological aspects of the component of mesodermal origin: A - cavernous-cystic vascular structures; B - osteo-cartilaginous and fibrocellular patches; C - lymphoid pseudofollicular structures; D - immature and mature cartilaginous mixed tissues associated with tubular glandular structures with epithelial dysplasia, mitosis and cysts in pseudomixomatous tissue.



**Fig. 8.** Tissue section of the excised specimen that demonstrates histological aspects of the component of endodermal origin: A - cysts lined with pseudostratified epithelium with columnar aspects in mesodermal components; B - cysts lined with goblet epithelium in differentiated connective fibrillar tissues

Along with the described changes, a predominant immature germ cell component (55%) was found, represented by glandular-alveolar tubular structures, sometimes in anastomosing cords of neoplastic cells, which had a primitive appearance, often polygonal and pleomorphic,

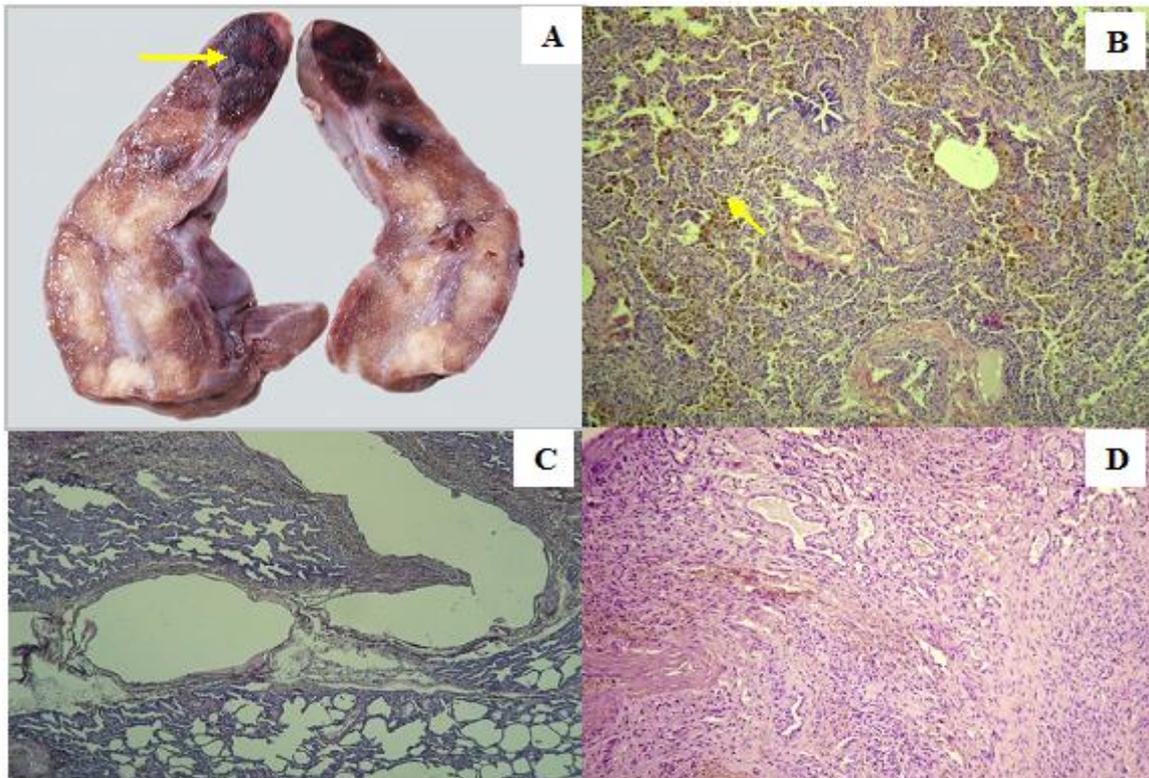
with hyperchromatic nuclei with activity. mitotic  $\leq 10$  to ob.20. Note the hyperplastic cellular peculiarities of the glandular-alveolar neoplastic structures of the stromal component and proliferative fusiformcellular character (fig. 9).



**Fig. 9.** Tissue section of the excised specimen that demonstrates the presence of embryonic carcinomatous malignant tissue-cellular elements with mitotic activity: A - alveolar germinal structures with minimal mitotic activity; B - atypical germ cell structures in conjunctival fibrillar component with dysplastic cell elements; C - germ cell structures with pleomorphism and cell mitosis; D - atypical germinal tubular cell islands with pleomorphic appearance with mitotic activity

In the resected lung tissue, the disorganization of the pulmonary lobular structures, the accentuation of the vascular network and congested areas with solid appearance were established. Histologically, a moderate hypertrophic-stenotic vasculopathy,

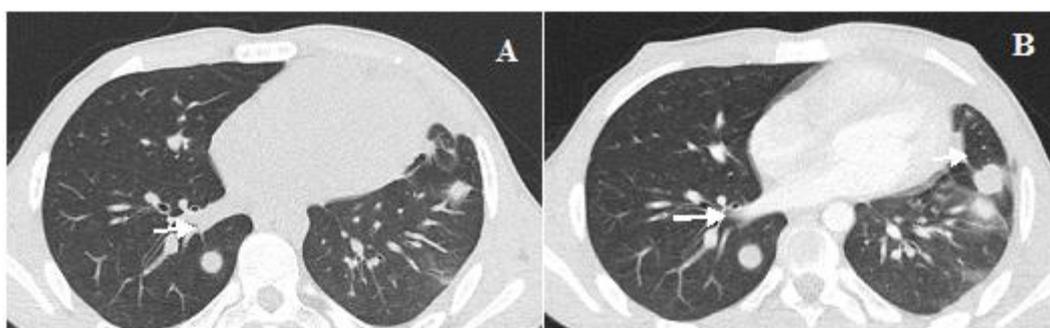
intralveolar sideromacrophagia, atelectasis, moderate distelectasis, foci of emphysema were found. In some areas vascular varicose ectasias could be attested, and in congestive foci nodular angiofibromatous changes were present.



**Fig. 10.** Tissue section of the excised lung specimen: A - solid congestive structures of the lung parenchyma; B - intra-alveolar sideromacrophagia, hypertrophic angiopathy; C - fusiform vascular cystic ectasia; D - pulmonary angio-fibromatous structures

Therefore, histological investigations suggested signs of mediastinal teratom with mature and immature components of ecto-, endo- and mesodermal origin, which alternated with structures of embryonic carcinoma, with perineural and lymphovascular invasion. In the resected lung sector, no neoplastic changes were found. Immunohistochemical tests found the following profile: tumor cells (malignant components of germ cells) positive for PCK, PLAP, OCT 3/4, C-KIT, EMA, SALL-4, D2-40 and negative for CD30, AFP, CEA.

The patient was discharged on the 10th day postoperatively. A postoperative CT evaluation at the time of discharge (12 days postoperatively) revealed a potential metastatic outbreak in the right lung and suspicion of an outbreak in the left lung (Fig. 11). Subsequently, the patient underwent chemotherapeutic treatment in a specialized institution according to the scheme: Cisplatin 30 mg 1-5 days, Etoposide 170 mg 1-3 days, Ifosfamide 2000 mg (+ Mesna) 1-5 days.



**Fig. 11.** Patient S. CT scan performed on the 10th postoperative day - suspicion of pulmonary metastatic foci (indicated by arrow)

## Discussions

Extragenital germ cell tumors are rare, being diagnosed starting with the neonatal period and in adolescents, the anterior mediastinum being the most common location involved in the neoplastic process<sup>[12]</sup>. It is assumed that the first description of a mediastinal teratom was made by Gordon, who in 1827 reported a tumor containing hair and teeth<sup>[4]</sup>. The term "teratom" was proposed by Virchow (1863) and comes from the Greek word "terrace", meaning monster and "oma" which means tumor<sup>[6]</sup>.

Benign teratomas are diagnosed at a younger age compared to malignant forms, the incidence of the latter being increasing with age. Mediastinal germ cell tumors in children and adolescents are characterized by a slow growth, with a symptomatology erased in the early stages, gradually reaching gigantic dimensions<sup>[13]</sup>. At the same time, cases are described when these tumors grow rapidly, reaching major dimensions even in young children<sup>[14]</sup>.

Most children with mediastinal germ cell tumors, including those with mediastinal teratocarcinoma, may be asymptomatic or have respiratory symptoms, chest pain, or signs of upper vena cava obstruction. The evolution of this neoplasm can be complicated by the rupture of the tumor in the pleural space, the tracheobronchial tree or in the pericardial sac. Increased chorionic  $\beta$ -gonadotropin levels may lead to the development of gynecomastia or hyperthyroidism, which in some cases may be the only manifestations of the disease<sup>[15,16]</sup>.

Multimodal imaging is important in the characterization and staging of mediastinal tumors. Computed tomography of the chest with contrast remains an option of choice, which together with the evaluation of serum levels of  $\alpha$ -fetoprotein, chorionic  $\beta$ -gonadotropin and lactate dehydrogenase allows an adequate diagnosis of mediastinal teratom with the degree of extension and invasion, topical relationship with vital structures. Nuclear magnetic resonance can also be used to identify the components of the tumor

formation and evaluate the surgical resectability. The definitive diagnosis can be established only at the histopathological examination, being performed a guided biopsy<sup>[3,17,18]</sup>.

In several neoplasms, vascular proliferation is found as a component of the tumor, which can be observed after chemotherapy treatment. Vascular proliferation, found in this case, is a rare feature that can mimic vascular neoplasm, being described in germ cell tumors, some of which are resistant to chemotherapy<sup>[19]</sup>.

The system of post-surgical staging of germ cell tumors in children differs from adults. According to the Child Oncology Group (COG), the post-surgical staging protocol includes:

- Stage I: complete resection with negative edges;
- Stage II: microscopic residual tumor or persistence of increased levels of tumor markers, with negative lymph nodes;
- Stage III: lymph node involvement, the presence of residual disease;
- Stage IV: distant metastases.

Stages I and II are considered intermediate risk, while stages III and IV are considered high risk<sup>[1]</sup>.

According to the MaGIC (Malignant Germ Cell International Collaborative) initiative, a combination of age, malignant tumor location and stage are the factors used in the risk stratification system. Under this system, low risk was defined for any age and COG I; standard risk 1 includes children <11 years of age and COG stage II-IV; Standard risk 2 includes children  $\geq$ 11 years of age and COG stage II; low risk includes patients  $\geq$ 11 years of age and COG stage III - IV. The objective of this stratification system was to identify patients with a reserved prognosis, who receive first-line therapy<sup>[1]</sup>.

The option of choice in the treatment of mature and immature teratomas is total surgical resection, which provides excellent overall survival. Mature teratomas do not require adjuvant therapy, while patients with immature teratomas require close monitoring in order to detect recurrences early. Patients with mediastinal germline malignancies have a poor prognosis, their treatment requiring

systemic chemotherapy based on cisplatin in combination with etoposide and bleomycin, radical surgical treatment and radiotherapy [13,20,21]. Treatment protocols for these types of tumors are described, which involve chemotherapy with Paclitaxel, Ifosfamide, and Cisplatin<sup>[22]</sup> or Etoposide, Ifosfamide, and Cisplatin<sup>[23]</sup>.

### Conclusions

This case confirms that in adolescence the teratocarcinoma of the anterior mediastinum is characterized by an extremely aggressive, fast-growing behavior, which in a short period of time can reach giant dimensions and advanced stages of the disease, as confirmed by the results of the examination. imaging and clinical-morphological investigations.

Germ media tumors of the anterior mediastinum represent a challenge for surgical treatment in connection with the particularities of tumor growth, location and topographic relationships to vital anatomical structures. Despite the complete ablation of the tumor with the lack of tumor extension outside the capsule and the lack of local postoperative recurrences, the risk of developing metastases in intrathoracic organs, found postoperatively, which are not always detected preoperatively, persists.

The use of argon plasma coagulator allows the tumor to be dissected safely, with minimal risk of hemorrhage, even in cases of intimate adhesion of the tumor capsule to adjacent anatomical structures.

The presence of a volume formation of the anterior mediastinum in male adolescents imposes the need for a greater degree of suspicion in the diagnosis of germ cell tumors.

The extensive histological examination of the excised specimen is very valuable in assessing the share of immature tissues and malignant germ components, in the case presented a large amount of embryonic carcinoma was identified, which, along with immature teratomatous components,

probably led to the aggressive evolution of neoplasm.

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