Mediastinal teratomas in children
Case reports and review of the literature

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BACKGROUND: In the pediatric age, mediastinal teratomas are an infrequent observation, accounting for only 7%-11% of extragonadal teratomas. Mainly located in the anterior mediastinum arising from the thymic gland, or exceptionally, from ectopic thyroid tissue, they may rarely be observed in the posterior mediastinum, sometimes in a paravertebral position, simulating a neuroblastoma.

The Authors have extrapolated, from their entire experience of teratomas, 3 cases, mostly operated as emergencies; 1 of them was treated just after birth. Aim of this paper is to report the clinical and pathologic findings, to evaluate the surgical approach and the long-term biological behaviour in these cases, in the light of survival and current insights reported in the literature.

MATERIALS AND METHODS: The Authors reviewed the most significant clinical, laboratory, radiologic and pathologic findings, surgical procedures, and early and long-term results in 3 children, 2 males and 1 female, suffering from extragonadal teratomas, located in the mediastinum, treated immediately after birth. In 1 of them the lesion was prenatally diagnosed by US scanning between the 2nd and 3rd trimester of pregnancy. All the infants were born by scheduled caesarean section in a tertiary care hospital and were then immediately referred to the N.I.C.U. because of a mostly acute clinical presentation. The 3 patients were referred to the surgical unit at different ages, namely 2 days, 10 years and 12.5 years, respectively. The initial clinical presentation was consistent with the site of the mass and/or its side-effects. The first patient, a female newborn, presented a worsening condition of respiratory distress, immediately after birth, that required mechanical ventilation and stabilization of the vital signs. Likewise, the presentation of case N° 2 was acute with dyspnea associated with an upper airways infection. Instead, the initial symptoms in case N° 3 were subacute and non-specific, characterized by worsening pain at the right shoulder extending to the neck and homolateral arm. The patients underwent laboratory and radiologic investigations that confirmed the clinical diagnosis of teratoma on the basis of elevated AFP values in 2 cases only (Case N° 1 and N° 2), while calcifications were lacking at imaging in all 3 patients. Emergency surgical management was required and, in accordance with recommended practice, the procedure was complete exeresis.

RESULTS: All the patients underwent close long-term clinical, laboratory and imaging surveillance at shorter intervals during the first 5 years after the exeresis and annually thereafter. At the present time they are alive, disease-free and have not suffered any recurrence and/or distant metastases, with a follow-up of 7, 30 and 3 years respectively.

CONCLUSIONS: Some extragonadal teratomas of childhood may rarely arise in the mediastinum. Being congenital tumors, prenatal diagnosis by US scan is extremely important in order to organize proper perinatal care in appropriate facilities where it is possible to define the diagnosis, and equipped with appropriate tools to carry out emergency surgery at minimal risk and to prevent severe complications after birth. An emergency procedure is frequently dictated both by complications related to the mass effect, and by the need to define the histology of the whole mass rather than just small
biopsy specimens. Some teratomas can hide more or less extensive islands of immaturity or signs of malignant transformation that are clinically evident. It should be noted that calcifications and high levels of AFP and/or beta-HCG, usually pathognomonic elements for diagnosis, may not always be evident during the diagnostic work-up in mediastinal lesions. The prognosis is generally benign, although the AIEOP 2004 guidelines pointed out that high levels of circulating markers, including AFP, in children affected by mature or immature teratomas would indicate the presence of micro-foci of YST, marking them out as at high risk. The UKCCSG II and the SFOP indicated AFP values exceeding 10,000 ng/ml as the threshold identifying a group of patients with a severe prognosis. The treatment indicated is early, complete exeresis, followed by a careful, extensive microscopic examination and associated, if necessary, with adjuvant chemotherapy. Finally, in accordance with recommended practice, close, long-term clinical, laboratory and imaging surveillance is necessary, at shorter intervals during the first 5 years after the exeresis.

**KEY WORDS:** Extragonadal tumors, Germ cell tumor, Mediastinal Teratomas

**Introduction**

In the pediatric age, mediastinal teratomas are an infrequent observation, accounting for only 7%-11% of extragonadal teratomas. Mainly located in the anterior mediastinum arising from the thymic gland, or exceptionally, from ectopic thyroid tissue, they may rarely be observed in the posterior mediastinum, sometimes in a paravertebral position, simulating a neuroblastoma. The Authors have extrapolated, from their entire experience of teratomas, 3 cases, mostly operated as emergencies; 1 of them was treated just after birth. Aim of this paper is to report the clinical and pathologic findings, to evaluate the surgical approach and the long-term biological behaviour in these cases, in the light of survival and current insights reported in the literature.

**Materials and Method**

We reviewed the most significant (Tables I, II) clinical, laboratory, radiologic and pathologic findings, surgical procedures, and early and long-term results in 3 children, 2 males and 1 female, suffering from extragonadal teratomas located in the mediastinum (cases N°1-3 – Figg. 1-3), treated immediately after birth. In 1 of them (Case N° 1), prenatal diagnosis was made by US scanning between the 2nd and 3rd trimester of pregnancy. All the infants were born by scheduled caesarean section in a tertiary care hospital and were then immediately referred to the N.I.C.U. Because of a mostly acute clinical presentation, the 3 patients were referred to the surgical unit at different ages: 2 days, 10 years and 12.5 years, respectively.

The initial clinical presentation (Table II) was consistent with the site of the mass and/or its side-effects. The first patient, a female newborn (case N°1- Fig. 1) presented a worsening condition of respiratory distress, immediately after birth, that required mechanical ventilation and stabilization of the vital signs. Likewise, the presentation of case n° 2 (Fig. 2) was acute with dyspnea associated with an upper airways infection. Instead, the initial symptoms in case N° 3 (Fig. 3) were subacute and non-specific, characterized by worsening pain at the right shoulder extending to the neck and homolateral arm.

**PHYSICAL EXAMINATION (Table II)**

At general examination the female 2-day-old newborn (Case N° 1), appeared critically ill, with cyanosis, dyspnea, nasal flaring, chest wall retraction, slight jugular distension, an evident swelling of the sternum associated with wheezing and grunting on expiration. The general conditions were good in the other 2 patients (Cases N° 2, 3), although the 10-year-old child (Case N° 2)
presented mild dyspnea associated with a slight distension of the jugular veins at admission. At the chest examination, a slight parasternal dullness on the right side was observed in both, but with noisy breathing sounds at auscultation only in Case N° 2.

LABORATORY
Blood-gas analyses showed a pattern of high grade respiratory acidosis in Case N° 1 and mild grade in Case N° 2. A high neutrophilic leukocytosis (WBC 20000/mm³, N 78%) with high values of inflammatory markers (ESR and CRP) was only observed in case N° 2. AFP values (Table I) were elevated in all except for Case N° 3, in which the Ca-125 value was rather high (78.1 U/ml - nv 0-30 U/ml). Other blood tests were normal.

IMAGING STUDIES
The selection of imaging studies was dependent on the clinical presentation. Radiologic assessment was based on antero-posterior (Fig. 1a) and lateral chest radiograph alone in Case N°1 because of severe respiratory distress. Plain chest scan or thoracic CT were added in cases N° 2, (1982, Fig. 2a-e) and N° 3 (Fig. 3a). Imaging demonstrated in each of these patients a heterogeneous non-calcified well demarcated anterior mediastinal density, bulging out from the mediastinum toward the right hemithorax. In the female newborn (Case n° 1) the mass appeared predominantly cystic and multilobulated. Most the cysts were quite large. In the early hours after delivery the cystic component suddenly enlarged, compressing the airway. In case N° 3 there was no confining border between the lesion and the thymic gland. An esophagogram and spirometry were also performed in the last case alone but yielded normal findings.

The imaging studies were a reliable and essential diagnostic tool for detecting the expansile lesion in all 3 cases, but because they lacked calcifications, imaging helped only to reveal the tumor location and also delineate the anatomy and relationship to the surrounding structures. Therefore, the clinical diagnosis of mediastinal teratoma was based on the elevated AFP values exclusively in Cases

<table>
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<th>Cases</th>
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<td>1. 2 days F (2005)</td>
<td>Respiratory Distress, Mechanical Ventilation</td>
<td>Cyanosis, Dyspnea, Nasal flaring, Chest wall retraction, slight jugular distension, Sternal swelling, Wheezing, Grunting on expiration.</td>
<td>Plain Chest Radiograph, Large cystic noncalcified opacity in the anterior mediastinum</td>
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<td>2. 10 y. M (1982)</td>
<td>Acute dyspnea during an upper airways infection</td>
<td>Mild dyspnea, slight distension of jugular veins, Right parasternal dullness with noisy respiratory sounds at auscultation</td>
<td>Plain Chest Radiograph + scan, Heterogeneous non calcified opacity in the anterior mediastinum</td>
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<tr>
<td>3. 12.5 y. M (2009)</td>
<td>Acute pain at right shoulder extending to the neck and homolateral arm</td>
<td>Mild dyspnea with “Upper mediastinal compartment Syndrome”</td>
<td>Plain Chest Radiograph + CT, Circumscribed heterogeneous mediastinal mass indistinguishable from the Thymic Gland</td>
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Fig. 1: Case N° 1: Age: 2 day-old female newborn 2005. a) Chest Plain X-ray: large non calcified well-demarcated cystic medium density opacity in the anterior mediastinum; b) Operative finding: predominantly cystic mass.
N° 1 and 2, while the diagnosis was suspected in Case N° 3 in view of the patient's age and localization of the lesion, while AFP values were in the normal range.

TREATMENT
Emergency surgical management was advisable in all the patients, owing to compression of the mass on the surrounding structures as a result of a sudden volumetric increase, as well as to the general risk of finding immature tissue or a malignant transformation from the usually benign type. The location and extent of the expansile lesion dictated the surgical approach, which consisted of: median sternotomy in cases N° 1 and 2, anterior right thoracotomy in case N° 3. In accordance with recommended practice, the procedure was complete exeresis of the mass.

PATHOLOGY
Based on the gross and histologic features the site of origin of the tumor was recognized as the thymic gland in case N° 3. Most lesions showed mixed solid-cystic features with a prevalence of the cystic component in the female newborn (Case N°1 - Fig. 1b). Applying the common classification system, all cases were classified as benign mature triphyllic teratomas, and as regards staging, all cases were Stage I.

RESULTS (Table I)
Close long-term clinical, laboratory and imaging surveillance was scheduled after the exeresis for all the patients, according to recommended practice. They are currently alive, disease-free and have not suffered any recurrence, with a follow-up of 7, 30 and 3 years respectively.
**Discussion**

The mediastinum is usually subdivided into the anterior, middle and posterior compartments based on the lateral chest radiograph. This arbitrary subdivision is extremely relevant in clinical practice because the compartments contain vital structures such as the heart, great vessels and airways, which can be compromised by expansile lesions. In fact, the mass effect can result in sudden life-threatening complications, such as the well-known “Critical mediastinal mass Syndrome” due to compression of any of these structures.

Although uncommon in children, mediastinal cystic and/or solid masses may arise in a variety of benign and malignant disorders. Hodgkin and non-Hodgkin Lymphoma and Neuroblastoma appear to be the most common etiologies of mediastinal masses in children: the former typically arise from the anterior or middle mediastinum, often associated with cardiopulmonary disorders, while the latter typically originate from the posterior mediastinum, rarely producing airways obstruction. Moreover, extragonadal teratomas located in the mediastinum have also been reported in the literature. These lesions are embryonal neoplasms which arise from an abnormal development of the primordial germ cells and/or embryonal totipotent cells, arriving there by abnormal migration or being primarily included. Like gonadal lesions, extragonadal lesions are encapsulated and contain tissues from the three germinal layers. These tumors sometimes exhibit a biologically bizarre behaviour. In fact, mature teratomas can have a malignant potential; malignant teratomas have shown a tendency to metastasise.
tasize. The rare form of teratomas with malignant transformation may not contain germinial malignant components but may be of somatic type, such as leukemia, cancer or sarcoma. In addition, a teratoma may present elements of other tumors with germinal cells, particularly YST, even in recurrent primary benign teratomas. These last lesions are considered mixed forms of teratomas; they behave like malignant teratomas and occur most frequently in infants and young children. Finally, a teratoma can be mature and non-malignant but highly aggressive, causing the well-known “Growing Teratoma Syndrome”.

In any case, extragonadal teratomas are characterized by their rarity, especially those located in the mediastinum, which are worthy of note for this reason.

The mediastinal localization of extragonadal teratomas is an infrequent observation in the pediatric age, accounting for only 7%-11% of these forms. Mainly located in the anterior mediastinum arising from the thymic gland, as in case N° 3, or exceptionally from ectopic thyroid tissue, they may rarely be observed in the posterior mediastinum, sometimes in a paravertebral position, simulating a neuroblastoma. The lesions are clinically characterized by a variety of presentations. They are often asymptomatic and incidentally discovered, but some patients are referred for an acute and dramatic manifestation, usually linked to complications such as the rare observation of rupture into the pleural cavity. Newborns may show the most dramatic presentation. That is characterized, in 35%-70% of cases, by severe respiratory obstruction due to a sudden enlargement of a predominantly or exclusively cystic teratoma, as in case N°1, as well as to compression of the mass on the surrounding structures, mainly in cases of heterogeneous lesions (cases N° 2, 3). Prenatal US scan can prevent early complications after delivery and may also detect both lethal lesions associated with fetal non-immune hydrops, and coexisting multiple malformations.

Moreover, prenatal assessment is essential to individuate the most logical, least invasive approach to the diagnostic work-up and to organize appropriate treatment. Sometimes the tumor is incidentally discovered, as in case N°2, during an acute upper airways infection or at radiographic assessment for persistent, worsening thoracic pain (case N° 3). High levels of the tumoral markers, particularly of α-fetoprotein, and the age of the child, are the only signs enabling a correct preoperative diagnosis of mediastinal teratoma, the typical calcifications being rarely evident at the imaging, as in our 3 cases. It must, however, be noted that AFP values may, in rare cases, even be normal (case N° 3).

An other distinguishing feature of mediastinal teratomas is the variability of the clinical course and their histology. All histotypes are possible and the clinical behaviour is generally benign, provided the exeresis is complete and carried out as early as possible. Microscopic investigation on the entire excised lesion can detect the coexistence of benign and malignant components, such as YST or the somatic type, that predisposes to the risk of local recurrence and/or distant metastasis. Therefore, diagnostic biopsy either by image-guided biopsy or by thoracoscopic or open surgery should be advised only for large lesions that are considered very difficult to resect.

Recurrences of primary mature benign teratomas containing malignant YST have already been described in the literature. Moreover, late surgery exposes the patient to various different risks such as spontaneous rupture and/or malignant transformation. On the other hand, even for rare immature lesions, accounting for only 1%, a benign course can be expected, but on the following conditions: a) complete exeresis, b) adjuvant chemotherapy to be administered, in accordance with Lakhou K et al. (1993), before surgery if the α-fetoprotein levels are high and after surgery if normal at the time of diagnosis; c) less than 50% of immature components inside the lesion. However, the prognostic factors widely recognized as valid for mediastinal teratomas include the location, age under 15 years and a lesser degree of immature components. Cases N°1 and N° 2 have not so far shown recurrences or distant metastases at 7 and 30 years after the diagnosis and exeresis (2005 and 1982, respectively), confirming that complete, early excision is mandatory for a favorable course, regardless of the presence of risk factors. The third case (2009) is also currently disease-free but the 3 years follow-up is still too short.

Conclusions

Some extragonadal teratomas of childhood may rarely arise in the mediastinum. Being congenital tumors, prenatal diagnosis by US scan is extremely important in order to organize proper perinatal care in appropriate facilities where it is possible to define the diagnosis, equipped with appropriate tools to carry out emergency surgery at minimal risk, and to prevent severe complications after birth. An emergency procedure is frequently dictated both by complications related to the mass effect, and by the need to define the histology of the whole mass rather than just small biopsy specimens. Some teratomas can hide more or less extensive islands of immaturity or signs of malignant transformation that are clinically evident. It should be remembered that calcifications and high levels of AFP and/or beta-HCG, although usually pathognomonic findings for the diagnosis, are not always evident during the diagnostic work-up in mediastinal lesions. The prognosis is generally benign, although the AIEOP 2004 guidelines pointed out that high levels of circulating markers, including AFP in children affected by mature or immature teratomas would indicate the presence of micro-foci of YST, marking them
out as at high risk. The UKCCSG II and the SFOP indicated AFP values exceeding 10,000 ng/ml as the threshold identifying a group of patients with a severe prognosis.

The treatment indicated is early, complete exeresis, followed by a careful, extensive microscopic examination, and, associated, if necessary, with adjuvant chemotherapy. Finally, in accordance with recommended practice, close, long-term clinical, laboratory and imaging surveillance is necessary, at shorter intervals during the first 5 years after the exeresis and annually thereafter.

### References


Commento e Commentary

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In questo articolo, Paradies e collaboratori riferiscono la loro esperienza con tre bambini (di 2 giorni, 10 e 12 anni di età) affetti da teratoma mediastinico. Due di questi pazienti (caso n. 1 e caso n. 2) sono stati trattati opportunamente come emergenze. Nel paziente n. 1 la diagnosi di presenza di una rilevante massa era stata fatta in fase prenatale, mentre nel paziente n. 2 l'accrescimento progressivo con compressione sugli organi adiacenti e conseguenti significativi sintomi respiratori avevano determinato un ricorso d'urgenza al ricovero ospedaliero.

Nel caso del neonato la pronta diagnosi e l'adeguato conseguente trattamento del voluminoso teratoma mediastinico era stato fondamentale per la diminuzione della morbilità e del rischio di una sua mortalità (caso n. 1). La diagnosi prenatale, infatti, consente il trattamento precoce delle malformazioni mediastiniche congenite, dato che la precoce asportazione della massa può essere effettuata ancor prima dell'insorgenza dei sintomi.

Sebbene l'ecografia prenatale sia molto utile per una migliore acquisizione e documentazione della massa, le eventuali difficoltà tecniche nell'ottenimento di immagini precise possono dar luogo a difficoltà interpretative dei dati. Pertanto la tomografia computerizzata o la RMN con mezzo di contrasto possono descrivere meglio i rapporti della massa con le strutture circostanti e l'eventuale presenza di localizzazioni multiple n. 2. La diagnosi definitiva è per lo più affidata all'esame anatomo-patologico postoperatorio.

Attualmente non c'è disaccordo circa l'indicazione al trattamento chirurgico del teratoma mediastinico, dato che manca qualsiasi trattamento medico. Comunque resistono alcune controversie circa i tempi operativi in assenza di condizioni d'urgenza, dovute alla mancanza di sintomi patognomonici.

Due pazienti sono stati trattati mediante sternotomia mediana ed uno con toracotomia antero-laterale con corrette moti-vazioni dipendenti dalla posizione anatomica della massa. Sebbene i chirurghi siano consapevoli che i teratomi mediastinici possono essere asportati mediante una sternotomia completa o parziale oppure con una toracotomia, alcuni ricercatori sono sostenitori della resezione toracoscopica robot-assistita per i teratomi mediastinici anteriori3. I vantaggi dell'approccio robotico insieme all'uso di strumentazione video-mediastinoscopica4 che permette una migliore percezione di profondità e un più ampio grado di libertà di movimento nella cavità toracica, permettendo una completa aderenza ai principi oncologici di resezione radicale con protezione delle funzioni e certamente questa tecnica merita di essere raccomandata a Paradies ad ai suoi collaboratori. L'uso del telescopio, infatti, rende possibile la visualizzazione del mediastino e permette di ottenere il controllo vascolare.

Infine le raccomandazioni interventistiche basate su questi pazienti, per una precoce e completa eseresi, e se necessario, per una chemioterapia adiuvante rappresentano attualmente una pratica standard. Inoltre nel caso di bambini un approccio multidisciplinare consente una migliore gestione di chirurgia oncologica in fase prenatale e post-natale.

Poiché si rende necessario un follow-up a lungo termine il dosaggio dell'alfa.fp rappresenta un valido elemento di sorveglianza nei confronti di una possibile recidiva.

Gli studi quali quello di questa esperienza, comunque, dimostrano quale risultato del progresso tecnologico i buoni risultati conseguiti con la chirurgia anche in bambini o neonati portatori di massa mediastinica. In futuro i rilevanti forniti dagli ultrasuoni diagnostici e dalla ricerca potrebbero eventualmente influenzare anche le indicazioni operatorie e le relative opzioni.

In this article Dr Paradies et al report their experience with 3 children (2 days, 10 an 12 y-o) patients with mediastinal teratoma. Two patients (case 1 and case 2) have been treated convincingly as emergency. In patient one the diagnosis of a large mass was performed prenatally while in patient 2 progressive growth and compression of adjacent organs with significant respiratory symptoms due to extrinsic compression determined the arising symptoms with urgent hospital admission1. The immediate detection and proper treatment of the large mediastinal teratoma in the neonate was most important to decrease the morbidity and mortality of the infant (case 1). Prenatal diagnosis in fact allows early management of congenital mediastinal malformations. Early resection can be performed prior to the occurrence of symptoms.

Although prenatally ultrasonography scan is a very useful tool for gaining a better understanding of and documenting the mass, technical difficulties associated with obtaining accurate imaging and the subsequent interpretation of the data obtained can arise. Therefore contrast thoracic CT-scan o MRI can better describe the relationship of the mass with surrounding structures, and the presence of multiple localizations 2. Final diagnosis is most of the time based on postoperative pathology.

Today there is a little disagreement about the indication for the surgical treatment of mediastinal teratomatas. As there is no medical treatment to remedy this condition. However, controversy remains about the timing of the operation when no urgent surgery is necessary, the reason for this lack of a consensus about the surgical treatment is the lack of patognomonie symptoms.
Two patients have been treated via a median sternotomy and one patient using an antero-laterale thoracotomy; the decision was correctly made on the basis of anatomical position of the mass. Although surgeons are aware that mediastinal teratomas can be excised via a partial, complete median sternotomy or a thoracotomy, some investigators recommend Robot-Assisted Thoracoscopic Resection of Anterior Mediastinal Teratoma. The advantages of a robotic approach associated with videomediastinoscopic instrumentation consisting of better depth perception and better range of motion in the chest cavity while still allowing adherence to oncologic principles of complete resection and preservation of function, and certainly this technique has to be recommended to Paradies and associates. The use of the telescope in fact enables the mediastinum to be visualized, and it also permits to obtain vascular control. Finally, the recommendations for operations which have been based on these patients consisting of early, complete excision and, if necessary, with adjuvant chemotherapy are now standard practice. Moreover in infants, a multidisciplinary approach allows more successful prenatal management and postnatal tumor surgery. As long-term follow-up is required, alpha-feto-protein can be a valid tool to monitor a possible recurrence. Studies like this report illustrate, however, that, as the result of technologic progress, surgery is now providing good results also in infants with mediastinal masses. In the future, the findings yielded by prenatal US and surgery may eventually influence also the therapeutic indications and options.

References
