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PICTORIAL ESSAY

PATHOLOGY OF THE THYMUS ON CT-IMAGING

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A number of masses arise in relation to the thymus. The radiologist has an important role regarding the differential diagnosis between non-tumoral thymic pathology and malignant thymic tumors. In general, a benign hyperplasia of the thymus occurs in children and young adults, while in adults the thymoma is the most common tumor. Furthermore imaging is of great importance in the preoperative staging and oncological follow-up. To evaluate the thymus CT scan is used in the majority of the cases. MRI or PET-CT can have an added value in the differential diagnosis of various thymic pathologies in some cases. We present an overview of thymic masses with typically imaging features: thymic hyperplasia, thymomas, thymic carcinoma, thymic non-hodgkin lymphoma, thymolipoma and thymic carcinoid.

Key-words: Thymus – Thymus, neoplasms.

From birth, the thymus increases in volume. It reaches its maximum volume around the age of eighteen. Then, the lymphoid thymus tissue will be replaced by adipose tissue. The thymus is sensitive to stress situations such as radiotherapy, chemotherapy, surgery, oncological diseases and generalized infections. In response to such stressful situations the thymus often atrophies. After the period of stress, the thymus grows to its normal size. In some cases, however the volume of the thymus may be even larger than before, called "rebound hyperplasia". Imaging is essential to avoid unnecessary invasive examinations such as mediastinoscopy with biopsy.

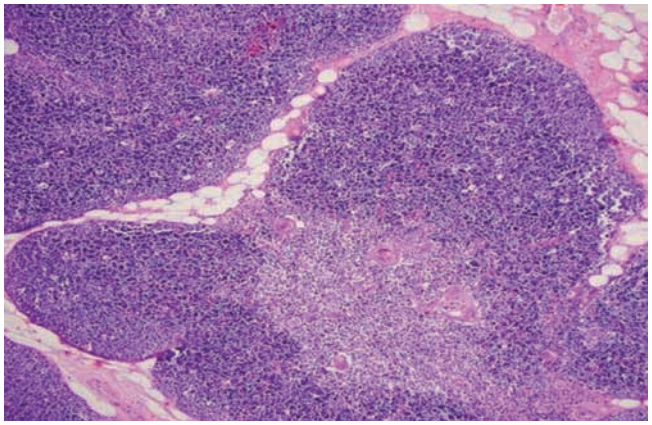

Fig. 1. — Histology of the thymus with hematoxylineosin stain (3). The photomicrograph shows the cortex, mainly composed of lymphocytes (thymocytes), and the medulla, mainly composed of epithelial cells.

Histology

The thymus is composed of two large lobes. Each lobe is divided into several lobuli. An interlobular septum separates the different lobuli from each other. Histologically, the thymus can be divided into a peripheral cortex and central medulla. The entity is surrounded by a capsule. The cortex of each lobule contains many lymphocytes (thymocytes). The medulla contains less lymphocytes, more epithelial reticular cells and Hassall corpuscles. Hassall corpuscles are oval structures, composed of a round or spherical aggregation of keratinized epithelial cells (1, 2).

Normal thymus

Function

The thymus is a crucial organ in the development of the immune system and plays an important role in the maturation of lymphocytes. Undifferentiated lymphocytes are transported through the blood to the thymus where the lymphocytes differentiates into immunocompetent T-lymphocytes. They provide the cellular immunity that triggers an immune response against intracellular micro-organisms (viruses, bacteria). The thymus produces various hormones, such as thymic humoral factor, thymulin and thymosin, necessary for growth, differentiation and maturation of T-lymphocytes (5).

Anatomy

The thymus is located in the upper anterior mediastinum, which is situated above the pericardium, behind the sternum, ventral of the aortic arch and the brachiocephalic vein. The upper border may extend to the lower pole of the thyroid gland. The lower border may extend to the diaphragm. The weight of the thymus at birth is 10 to 15 g. The maximum weight around puberty is 10 to 50 g and the weight reduces to 5 to 10 g at old age. The thymus has a pink-gray color in children and a yellow color in adults (3, 4).

The thymus reaches its maximum size and weight around puberty. Subsequently, the lymphoid tissue is progressively replaced by adipose tissue. Accordingly, the thymus decreases in size and weight. For a

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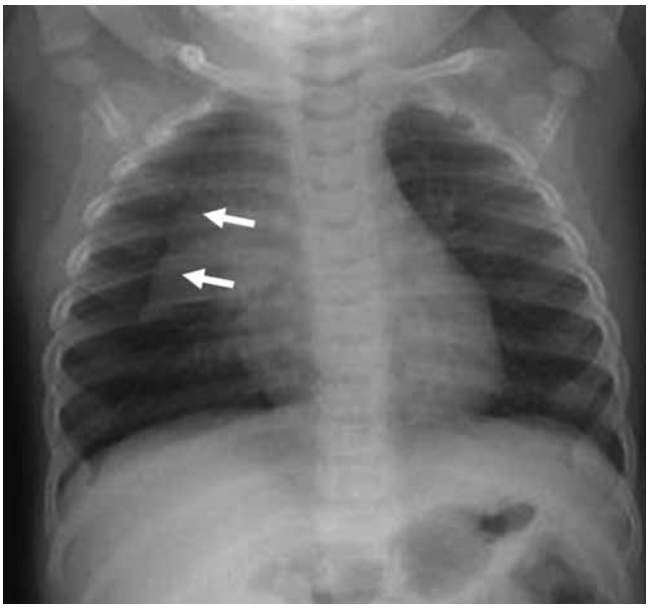

Fig. 2. — PA chest radiograph shows a typical thymic sail sign *(arrow)* in a 6 mounths old female with mild respiratory distress.

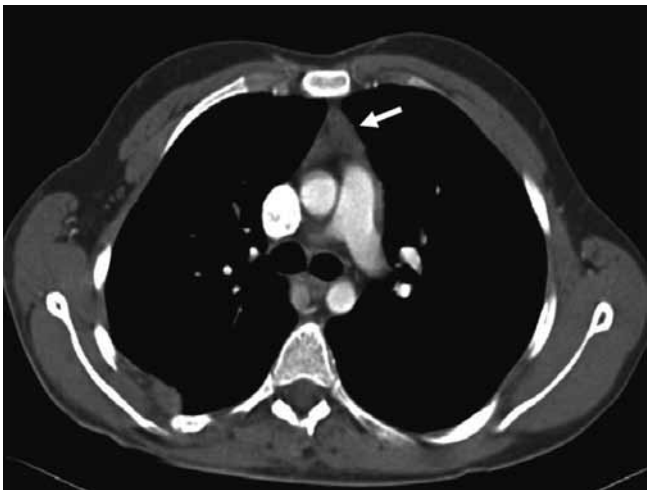

Fig. 3. — Normal thymus in a 27-year-old patient. The thymus appears triangular and of soft tissue attenuation, the left lobe being larger than the right *(arrow)*.

radiologist, it is important to identify the location, size and shape of the thymus over time to recognize or exclude pathologies (5, 6).

Chest radiograph shows a triangular sail-shaped shadow above the heart, left of the midline, called a 'sail sign' (Fig. 2) (7). This shadow will decrease progressively. In adolescents and adults the normal thymus is not visible. CT scan is the standard procedure in the diagnosis of mediastinal pathologies. CT images of the normal thymus change in function of age. From birth to puberty, the density of the thymus corresponds at CT to skeletal muscle. From puberty to 30 years both the shape as well as the density of the thymus will change on CT image. The density will decrease as a result of increased fat infiltration and is clearly lower than skeletal muscle. After the age of 30 years, the thymus progressively evolves to an atrophic linear or oval structure with fat density. At CT, it is hence difficult to distinguish the thymus from the mediastinal fat (3, 8). CT shows a bilobulated, triangular opacity in the anterior mediastinum with a maximum thickness measured in transverse axis (< 20 j: 1,8 cm; > 20 j: 1,3 cm). The left thymic lobe is usually larger than the right lobe (Fig. 3) (3). Imaging of the thymus using MR shows on T1 weighted images homogeneous, intermediate signal intensity, being less intense than surrounding mediastinal fat. On T2 weighted images, the signal intensity resembles to the signal intensity of fat. In patients over 30 years of age, differentiation between the thymus and adjacent mediastinal fat may be difficult because of thymic involution (9).

Disorders of the thymus

Thymus hyperplasia

Histological thymus hyperplasia can be classified into two types of hyperplasia: true thymic and lymphoid (follicular) hyperplasia (13).

The gland typically enlarges and gains weight. This form of hyperplasia is found in patients recovering from an acute stress period. Depending on the duration and severity of stress there will be in first a thymic atrophy of 40% of its volume. Afterwards the thymus can grow back to its normal size or even 50% above its normal volume. This phenomenon is called thymic rebound hyperplasia, which mainly occurs after serious illnesses or treatment (e.g. pneumonia, prolonged treat-

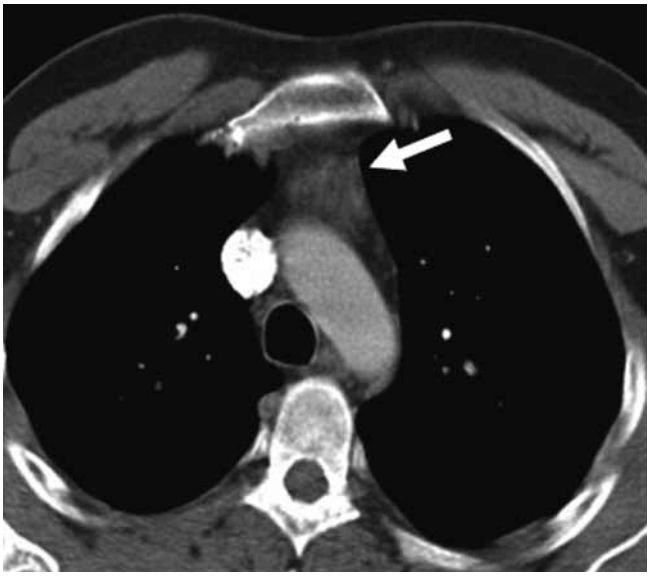

Fig. 4. — Thymic hyperplasia in a 26 year old boy who completed chemotherapy for testis carcinoma. CT shows enlargement of the thymus in the prevascular space *(arrow)*.

ment with corticosteroids, radiation or chemotherapy) (Fig. 4) (8, 10). This form of thymic hyperplasia is also found in conditions such as hyperthyroidism, sarcoidosis, or red blood cell aplasia (13).

Lymphatic (follicular) hyperplasia is characterized by an increase in lymphoid follicles, lymphocytes and plasma cells in the medulla of the thymus. This type of hyperplasia occurs in 65% of the cases with Myasthenia Gravis (14) and is also seen in connective tissue diseases or in the early stage of Acquired Immune Deficiency Syndrome (7).

Thymic hyperplasia appears in the majority of cases as a diffuse, symmetrical enlargement of the thymus in the presence of fat and lymphatic tissues. The thymus is clearly defined and the surrounding blood vessels are normal. The presence of lymph node enlargement in association with thymic enlargement should suggest pathology, while isolated thymic enlargement should suggest thymic rebound hyperplasia. On MR, patients with thymic hyperplasia or thymic rebound may show enlargement of the thymus, but its signal intensity is the same as for normal thymus. There is no difference on inmaging between thymic rebound hyperplasia and lymphatic hyperplasia (7, 9).

The normal thymus shows no tracer activity on Positron Emission Tomography scan (PET scan). Thymic rebound hyperplasia is seen routinely on follow-up PET studies of patients with neoplasms and should not be confused with a pathologic condition (10, 11, 12).

Cysts of the thymus

A thymus cyst may originate congenitally or can be acquired after trauma, chemotherapy or thoracotomy. The cysts are lined with epithelium, can be uni-or multilocular and calcifications in the wall may occur. Cysts are also seen in 40% of patients with a thymoma.

A cyst of the thymus presents itself as a well-defined anterior mediastinal mass that may extend into the neck region on frontal chest radiograph (7). CT shows a uni- or multilocular thin-walled homogeneous defined mass with water density. Bleeding or calcifications can be found. The size can vary from several mm up to more than 15 cm (7). Contrast-enhanced CT (CE-CT) shows a thymic cyst as a nonenhancing low-density cystic mass. The MRI signal depends on the contents of the cyst fluid, with proteinaceous or hemorrhagic material appearing hyperintense on T1-weighted images (10).

Tumors of the thymus

A. Epithelial tumors: thymoma and thymus carcinoma (Fig. 5)

Thymoma is a slow growing tumor originating from the epithelial cells of the thymus. Thymoma is the most common primary thymic tumor and accounts for about 20% of primary mediastinal masses. The incidence is equal for men and women. It is most common in patients aged 50 to 60 years. Thymomas are often asymptomatic, but 20-30% have symptoms related to compression of mediastinal structures. There can be an association with autoimmune diseases such as myasthenia gravis, lupus, rheumatoid arthritis and Crohns disease. Thymomas can be fully encapsulated or invasive (15). Invasive thymomas are histological identical to encapsulated thymomas but are locally aggressive and invasive in the tumor capsule and adjacent structures, including pericardium, pleura, superior vena cava, great vessels, airways and heart. Thymoma rarely metastasizes outsite the thorax (7, 16).

Chest radiograph shows a sharply marginated, smooth or lobulated mass in the anterior mediastinum, best seen on the lateral projection. They typically range in size from 5 to 10 cm in diameter when visible on radiographs and may obscure the right or left heart border, depending on their location and size. Calcifications, mass effect or pleural effusion can be found. The evaluation of invasion with conventional imaging is not possible (7). Thymoma presents on CT as a uni- or bilateral mass replacing the normal arrow-shaped thymus in the prevascular space. They usually shows homogenous attenuation on CE-CT. Cysts, calcifications, hemorrhage or necrotic parts can be detected on CT. Invasive thymomas are poorly delin-

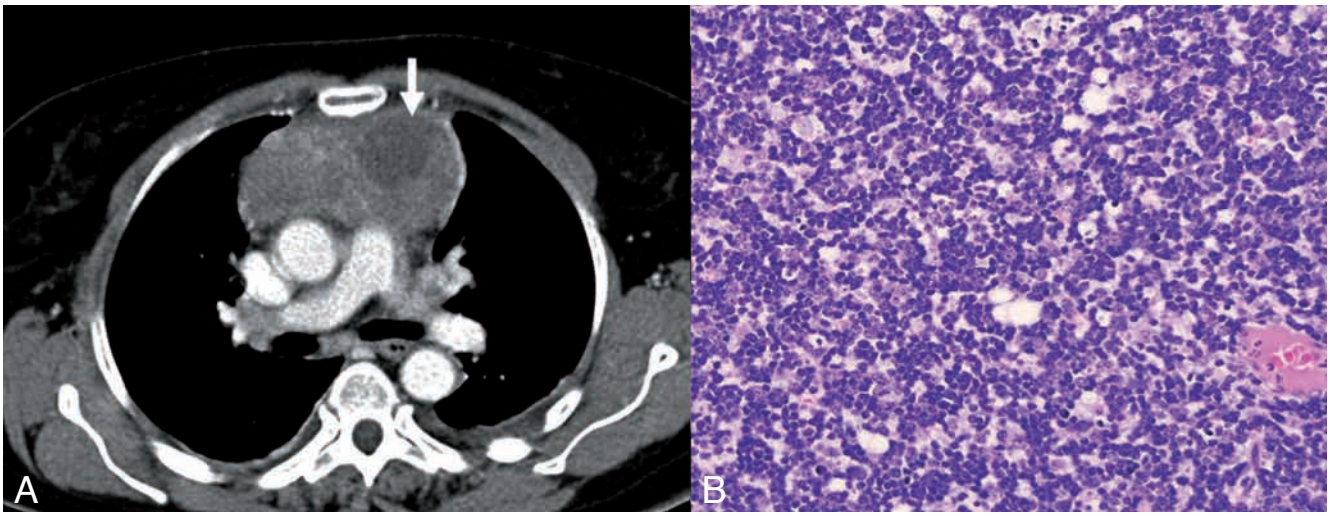

Fig. 5. — A. Stage I thymoma. A 70-year-old woman complaining of prolonged chest pain was seen in the emergency room. CT shows a sharply defined soft tissue mass with fatty componants of 10.2 cm × 4.5 cm × 4.9 cm in the upper anterior mediastinum. At the left side there is a more cystic / necrotic zone *(arrow).* This mass caused a partial compression of the vena innominata (not shown on this image). Neurologically there were no arguments to withhold the diagnosis of Myasthenia Gravis.

B. APO: a lymphocyte-riche, non-invasive, encapsulated (cortical) thymomas.

Table I. — Staging of thymomas according to Massaoka et al (3, 17).

Stadium			TNM
I		Encapsulated tumor	T1
II	A	Microscopic capsular invasion	T2
	B	Macroscopic invasion into adjacent fat tissue	
III	Macroscopic invasion into adjacent organs		T3
	A	Without invasion into large vessels	
	B	With invasion into large vessels	
IV	A	Pleural or pericardial dissemination	T4
	B	Lymphogenous and hematogenous metastasis	

eated with an absence of surrounding rim of fat, fixed pleural nodules (drop metastasis) and pleural or pericardial effusion. Distant metastasis is rare (15, 17). There is no specific MR signal for thymomas. They may appear homogeneous in intensity or inhomogeneous with or without cystic components or low-intenstity septations. An inhomogeneous signal intensity with an apparent lobular internal architecture indicates malignancy. MR signal can be used to diagnose vascular invasion, especially in patients with contraindications for intravenous contrast (9).

Thymomas can be staged at the time of surgery. The most recent classification of Massaoka et al. (9) is preferable for staging thymomas. The classification is based on the capsular penetration and the invasion of adjacent structures (17).

Thymic carcinoma (Fig. 6, 7) arises from thymic epithelial cells, as in thymomas, but they behave more aggressively than thymomas and are more likely to metastasize. Histological examination is essential for the differential diagnosis between thymomas and thymus carcinomas. It is difficult on CT imaging to distinguish a thymus carcinoma with an invasive thymoma (18). Almost pathognomonic for thymus carcinomas are thymic masses with mediastinal lymphadenopathy, vascular or pericardium invasion, vena cava superior syndrome and distant metastases at diagnosis (17) (Table I).

Chest radiographs can show large, irregular marginated, lobulated mass at the level of the anterior mediastinum. CT demonstrates a large, irregular, multilobulated heterogeneous mass with hypodens areas (e.g. necrotic or cystic areas). There is a poor delineation and local invasion of mediastinal vessels in 40% of cases. Furthermore calcification, hemorrhage can be found, as well as mediastinal lymph node enlargement, invasion of the pericardium and the pleura. Distant metastases are present at diagnosis in 50-65% of patients (9, 17). Thymus carcinoma shows on MR imaging a high signal intensity on T1 and T2 weighted images. Heterogeneous signal may reflect the presence of necrosis, hemorrhage or cystic regions within the tumor (7).

FDG-PET can be useful in differentiating thymic carcinoma from invasive or non-invasive thymomas. Sasaki et al. (17) reported that the standardized uptake value (SUV) for thymic carcinoma is significantly higher than thymomas. FDG PET can not differentiate between invasive and noninvasive thymomas (27).

B. Hodgkin and non-Hodgkin lymphomas (Fig. 8)

Lymphomas in children are one of the most common masses at the level of the anterior mediastinum. Degradation of the thymus by a lymphoma usually occurs in the context of systemic diseases. A primary lymphoma of the thymus may also occur. The thymus is enlarged by diffuse infiltration. Sometimes a

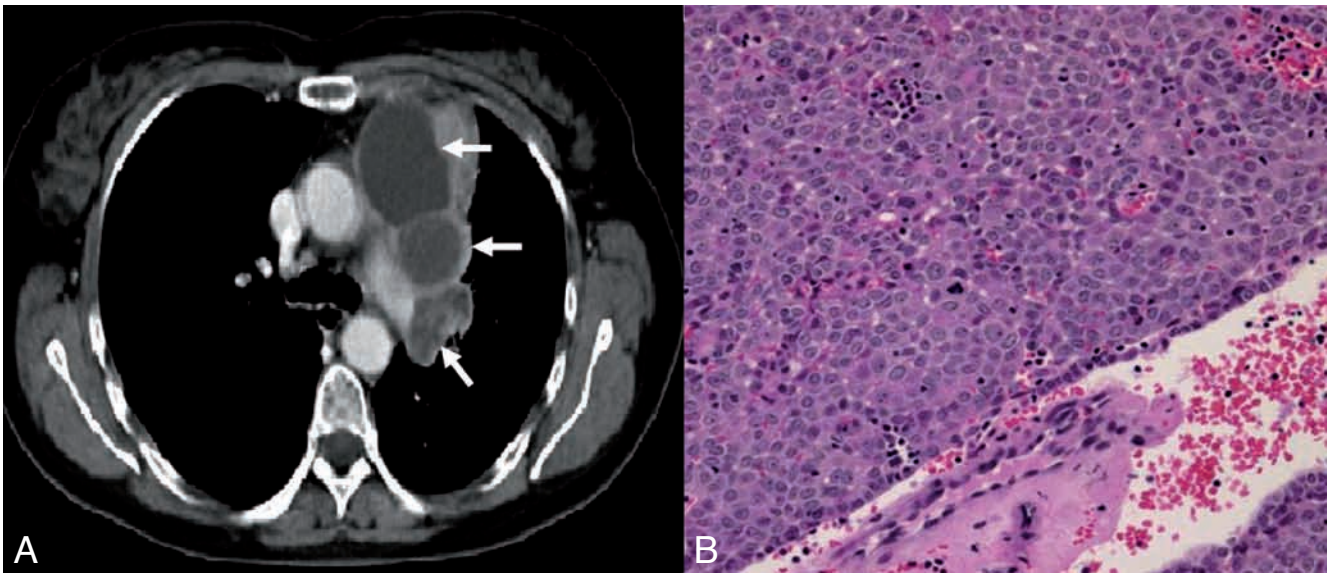

Fig. 6. — Thymic carcinoma. A) A 61-year-old woman consulted the pulmonary specialist because of cough and hoarseness. CT showed a large suspicious process above the left hilus in the anterior mediastinum. The mass contained central necrotic and cystic areas *(arrow)*. Laterally there is a tissue board and the medial border of the process is inseparable of the ascending aorta. B) APE: Epithelial cells with nuclear atypia and many mitosis: good to moderated differentiated squamous cell carcinoma of the thymus (20).

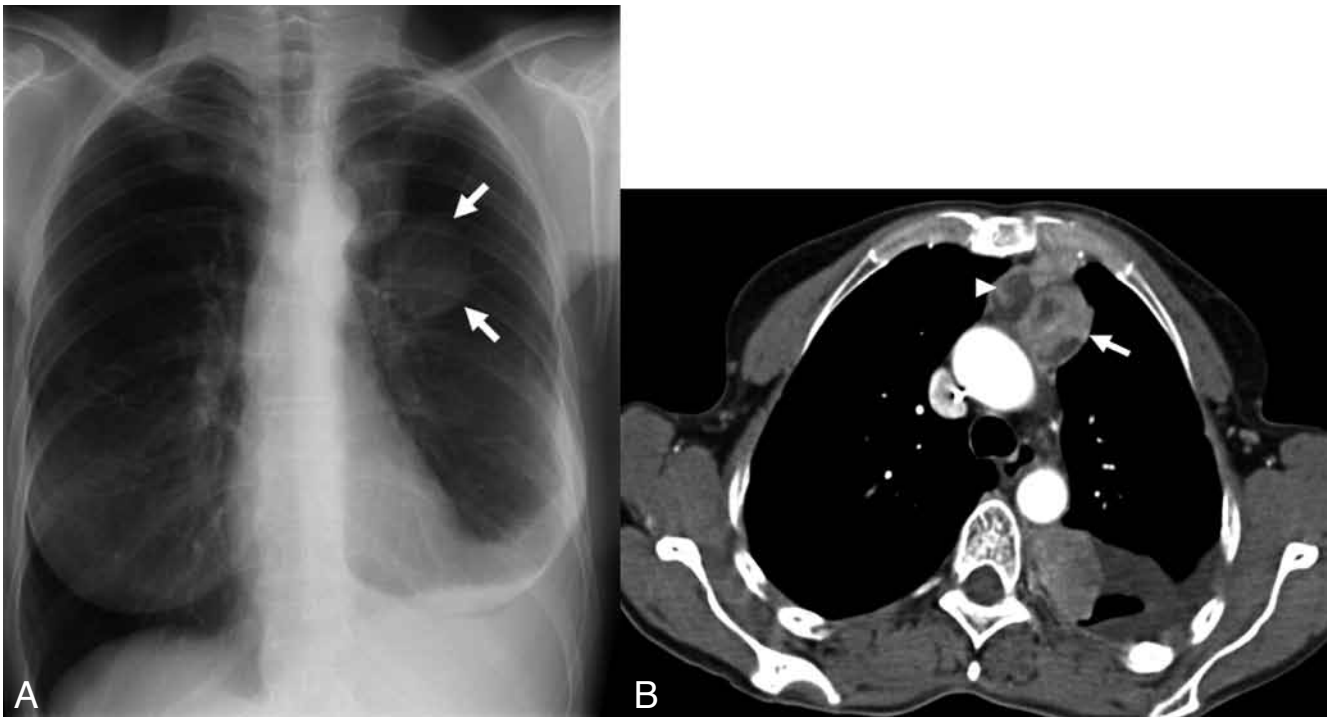

Fig. 7. — Thymic carcinoma. A. Thymic carcinoma in a 50-year-old woman with weight loss and coughing at night. PA chest radiograph shows a smooth, sharply marginated left mediastinal mass (*arrows)*. B. CT showed a mass in the left anterior mediastinum with enhancement following contrast infusion *(arrow)*. The mass contained central necrotic and cystic areas *(arrowhead)*.

solitary mass or multiple masses can be noticed. Lymphoma depletion of the thymus occurs mainly with Hodgkins disease. Thymus invasion by non-Hodgkins lymphoma is rare (13).

Solely based on imaging, it is difficult to make a differential diagnosis between a primary thymus lymphoma and a thymoma. Thymus lymphomas are more common in younger patients. Lymphomas of the thymus usually behave more aggressively than thymomas, but respond well to the chosen therapy (radiotherapy and / or chemotherapy). After adequate treatment thymus lymphoma usually disappears completely (20). On imaging, a remnant of soft tissue density can be seen, representing fibrosis (21). A new increasing mass usually indicates "rebound thymic hyperplasia", but a recurrence of a thymus lymphoma should be excluded. "Thymus rebound hyperplasia" shows distinctly a diffuse, symmetri-

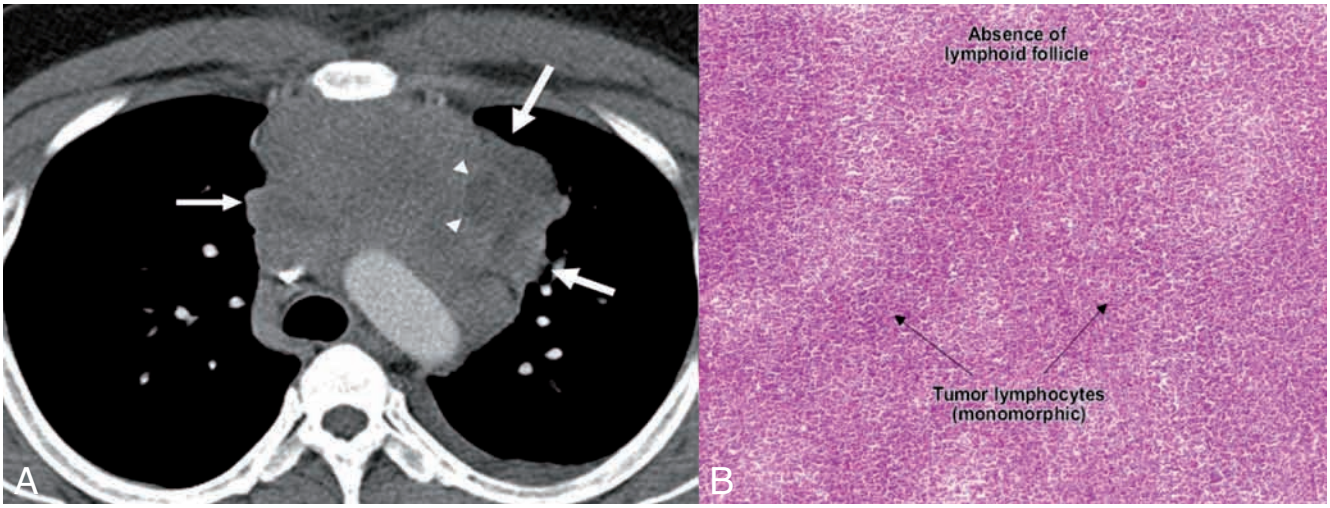

Fig. 8. — A. Thymus non-Hodgkin lymphoma with superior vena cava compression. A 35-year-old patient with blank history was seen at the emergency service in response to pain and swelling at the left shoulder and left arm. The patient had no chest pain nor weight loss or haemoptysis. CT scan showed a heterogeneous, contrast capt masses in the anterior upper mediastinum with cystic and necrotic zones *(arrowhead)*. The masses had irregular edges and maximum diameters of + / - 9 cm × 7 cm × 8 cm *(arrow)*, nearly related to the pars ascendens and the arcus aorta. B. APO: Architecture of the lymph node was replaced by proliferation of tumor lymphocytes (immature, monoclonal). Primary B-cell non-Hodgkin lymphoom.

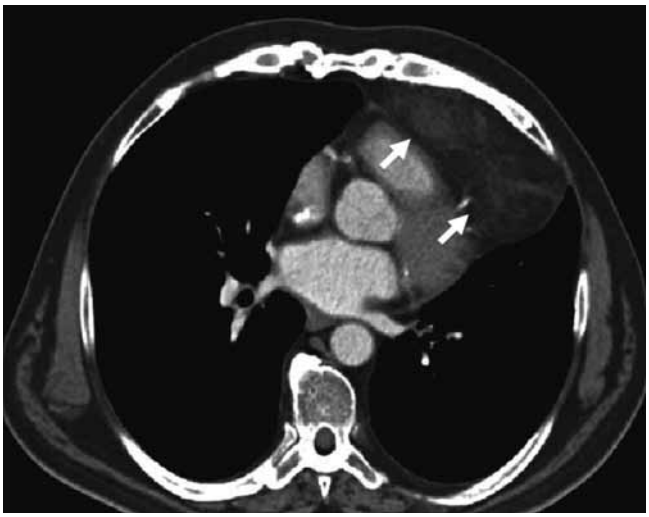

Fig. 9. — Thymic lipoma. A 59 year old men is known with a spinocellular bronchial cell carcinoma. CT scan with contrast shows a mixed fatty and contrast captated solid tissue mass located left paracardial in the anterior mediastinum *(arrow)*. (ca. 10 × 5 × 7 cm).

cal enlargement, with the presence of fat and lymphatic tissue, clear delineation and normal blood vessels on CT imaging. A recurrent thymus lymphoma, on the other hand, is rather asymmetrical, irregular marginated and nodular (7).

On chest radiograph a lymphoma causes an anterior mediastinal mass with thin linear calcifications and pleural effusion. An asymmetric, homogeneous enlargement of the thymus is seen on CT imaging. Presence of mediastinal and/or hilar lymphadenopathies is usually visible. In 20% of the patients calcification, hemorrhage or cystic changes are present. MR T1 weighted images of the thymus shows a homogeneous signal intensity of muscle. On T2 weighted images, the thymus corresponds to an equal or higher signal intensity than the signal intensity of fat tissue from tumor edema, inflammation or granulation tissue (9).

Histological examination of a lymphoma shows typical Reed-Sternberg cells in a background of lymphocyts, macrophages, fibroblasts and granulocytes (7).

CT scan is the best modality for initial staging and follow-up for Hodgkin lymphoma (13, 22).

C. Thymolipoma (Fig. 9)

Thymolipomas are rare, benign, slow growing tumors, consisting of normal thymic tissue and fat. The incidence is the highest among young adults. They are found in equal percentages of men and women. Usually they are very large and may reach a diameter of 20 cm. Thymolipomas causes compression symptoms in about 50% of cases but do not invade surrounding structures. They are usually discovered by accident during a routine inspection or radiological examination (9, 23).

Radiographic finding of thymolipoma is a large mass in the anterior mediastinum that can imitate an elevated diaphragm or cardiomegaly. CT imaging shows a large, sharply demarcated fat mass with septa. The mass consists of 50%-85% fat (8). T1- and T2-weighted images show high signal intensity in areas of fat in thymic tissue. The lines of low intensity on (T1 / T2 or both) indicate fibrous septa (9).

D. Carcinoid tumors (Fig. 10)

The carcinoid tumors are well-differentiated neuroendocrine tumors with a low degree of malignancy. 20% of thymus tumors are carcinoïd

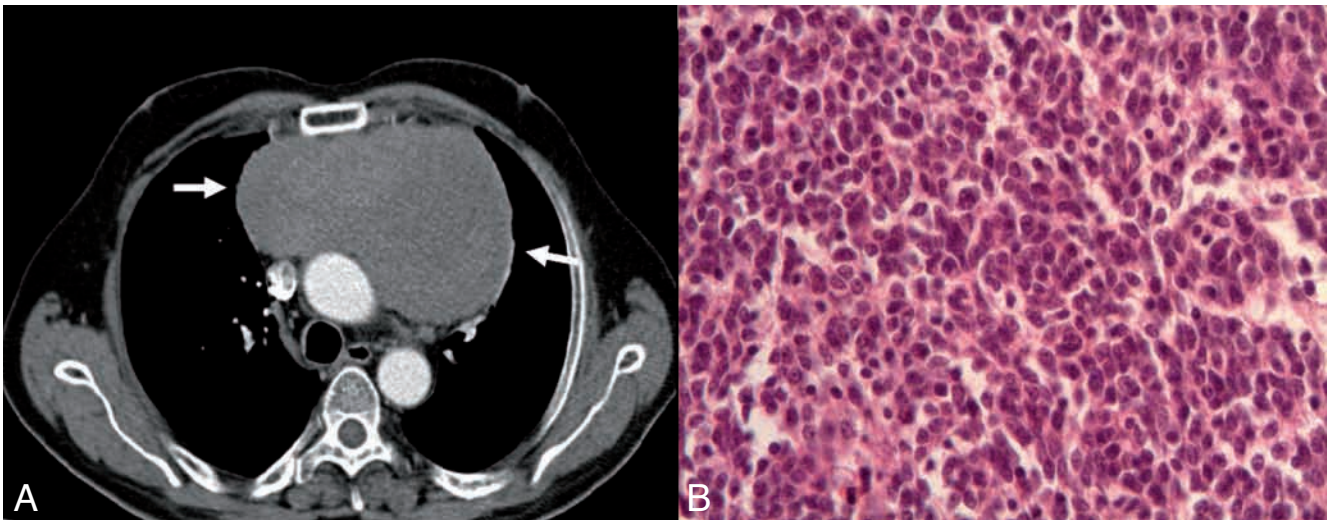

Fig. 10. — Thymic carcinoïd. A 59 year old man logs on to the emergency department because of chest pain, chronic cough and weight loss. Thoracic CT shows a large voluminous inhomogeneous solid mass with a diameter of 16 × 9 cm. There are no calcifications, cystic necrotic areas, invasion of vascular structures and no pathologically adenopathies *(arrow)*.

Patient was operated and postoperatively treated with chemotherapy and radiotherapy.

APE: thymic carcinoid tumor: the typical carcinoid cells are small basophilic cells with a typical growing pattern in a carcinoid: rounded nests of cells = "Zellballs"; "microrosettes" of cells can also form. The cells have a round small central core and a eosinophilic granular cytoplasm. The chromatin of the nucleus is finely grained. The mitotic activity is limited and not very pronounced (Courtesy: AZ Monica).

tumors. The incidence is three times higher for men than for women. In most cases they are asymptomatic. However, in 1/3 of cases these tumors are functionally active. Besides compression symptoms, endocrine manifestations may occur in which an increase in adrenocorticotropic hormone (ACTH) causes the Cushing's syndrome (e.g. rapid weight gain, buffalo hump, moon face, hyperhidrosis, telangiectasia, purple or red stiae).

Thymic carcinoid tumors are more aggressive than thymomas and often cause the superior vena cava syndrome. 20% of these tumors are associated with type 1 MEN syndrome (8). In 50% of cases they are already invasive at the time of diagnosis (9, 13).

Chest radiograph shows mostly large masses (10-15 cm) in the anterior mediastinum with poor demarcation (22). Irregular areas of necrosis or hemorrhage and fine calcifications are found on CT. The findings mimic those of thymomas. Metastasis to lungs, pleura, brains and lymph nodes occur in 50% of thymic carcinoid tumors at the time of diagnosis (7, 22).

It is not possible to determine the differential diagnosis between an invasive thymoma and a carcinoid tumor based on imaging alone (8, 22).

E. Germ cell tumors

More than 80% of mediastinal germ cell tumors are benign and do not have a gender preference (6, 9). The malignant forms are more common with men, with peak prevalence around 30 yr of age. Germ cell tumors are responsible for 1% of the malignancies in men. The most frequent extragonadal localization of germ cell tumors is mediastinal. In a mediastinal localization, an underlying primary testis localization must always be excluded. The germ cell tumors are divided into teratomas, seminomas and non-seminomas germ cell tumor (24). Teratomas are the most common germ cell tumors in the mediastinum. They may present in various forms: immature, mature and malignant. The teratomas can cause symptoms such as cough, dyspnea and chest pain by pressure (6).

Teratoma presents on chest radiograph in the anterior mediastinum projecting to one side of the mediastinum. Calcifications is visible in about 25% of the patients with teratomas. Teeth and bone are diagnostic but rarely seen (24). CT imaging shows a lobulated, cystic mass with varying thickness of the wall and calcifications. Benign teratomas contain 75% of fat tissue. In case of malignant teratomas, the mass will consists of 40% fat tissue. Mature teratomas are smooth or lobulated and have solid or cystic abnormalities. Malignant teratomas are poorly delineated masses with necrotic areas and bleeding (20). Heterogeneous signal due to composition of fat, soft tissue, hemorrhage and calcifications are demonstrated on MRI imaging. Detection of fat in adjacent structures through invasion in the pericardium, lungs and pleural space is seen with 33% of patients.

The seminoma and non-seminoma germ cell tumors occur less frequently than teratomas.

Chest radiograph of a seminoma shows a large lobulated, homogeneous mass. Invasion or calcifications are rare. Non-seminoma presents as a large irregular, heterogeneous mass with necrotic areas and bleeding. Frequent pulmonary metastasis, pleural and pericardial effusion are detected (3, 21, 24). With medical imaging (CT and MRI) alone, it is not possible to determine the differential diagnosis between germ cell tumors and thymomas. Histological examination is usually required. Thymomas occur more frequently in the elderly and are often associated with paraneoplastic syndromes such as myasthenia gravis (1).

F. Langerhans cell histiocytosis

Langerhans cell histiocytosis is a disorder characterized by clonal proliferation of Langerhans cells that move from the bone marrow and end up in the skin or lymph nodes. The symptoms can be diverse and depend on the place of occurrence and the extent of the disease. Multiple organs may be affected. Histiocytosis frequently leads to the deterioration of the thymus. On radiological imaging, an enlarged mass in the anterior mediastinum will be found. The thymus may have both a nodular and a lobulated appearance. Often, multiple calcifications occur in the thymus. After treatment with chemotherapy, a reduction or even disappearance of these features is observed on CT imaging (7).

G. Sarcoma

Sarcomas of the thymus are extremely rare. CT and MRI show a homogeneous, low fatty content mass. Differentiating with lymphoma or other primary tumor of the thymus is difficult. The prognosis of sarcoma of the thymus is very poor (25).

H. Metastasis

Metastasis at the level of the thymus is rare. Through lymphatic path, tumors of the head and neck, abdomen and pelvis can invade the thymus. Some lung tumors or mediastinal tumors can invade the thymus locally (2, 24).

Conclusions

Both benign and malignant tumors of the thymus are uncommon. A benign hyperplasia of the thymus generally occurs in children and young adults. A thymoma however is the most common tumor in adults. Radiological imaging is essential for the diagnosis and monitoring of thymic tumors. Accurate knowledge of the anatomy and evolution of the volume of the thymus in time is essential to ensure a correct interpretation of radiological images.

In most cases, a mediastinal mass is discovered accidentally on a plain X-ray and appears as a soft tissue opacity. Using conventional radiography, it is impossible to make a correct differential diagnosis (10).

CT scan is the best modality for diagnosing, preoperative screening and follow-up of mediastinal tumors. Literature shows that CT scan has a sensitivity of 91% and a specificity of 97% in the diagnosis of anterior localized mediastinal masses (9). The CT imaging appearance of the mass (fat - water density) is of great importance in the differential diagnosis. Increased fat density appears especially in teratomas and thymolipomas. CT scan is sensitive to show capsular breakthrough or local invasion in vascular structures, the pericardium or pleura (26). The presence or absence of capsular breakthrough or invasion is an important prognostic factor for thymoma and thymic carcinoma (3, 10, 17).

The role of MR in diagnosing thymic masses is limited. MRI is very sensitive to confirm fat in thymic tissue. Moreover the diagnosis of thymolipoma on MRI is superior to CT scan. MR imaging may also be useful in differentiating between thymomas and thymic cysts that demonstrate increased CT attenuation due to hemorrhage (3). In some cases MRI is more suitable to visualize vas-

cular invasion or thrombosis. Especially in patients to whom intravenous contrast cannot be administered MRI is the medical imaging technique of choice (9, 24).

The normal thymus shows no tracer activity on PET scan. However, it may show striking FDG avidity in rebound hyperplasia, causing false alarm. FDG PET may be useful in differentiating thymic carcinoma from other thymic neoplasms, thymic hyperplasia and normal physiologic uptake (27). The standardized uptake value (SUV) for thymic carcinoma is significantly greater compared to thymomas. Differentiating between invasive and noninvasive thymomas is not possible (3, 20, 27).

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