Revisiting a Forgotten Organ: Thymus Evaluation by PET-CT

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Abstract
Incidental thymic lesion findings have increased. An adequate characterization of these lesions in positron emission tomography/computed tomography (PET-CT) is essential, since it is used as part of many oncological planning procedures. Representative cases have been selected regarding the most important aspects of thymus imaging in PET-CT and how this technique can contribute to an accurate diagnosis or treatment planning.
Specifically, we present a general description of common thymic lesions and and simulated thymic disease, with an emphasis on PET-CT findings, also incorporating examples of magnetic resonance imaging (MRI).

Keywords
Thymus gland, thymus neoplasm, positron emission tomography/computed tomography

Introduction

The thymus is a lymphoid organ that plays an essential role in the development and maturation of the immune system, especially of T cells, during childhood.[1] Thymic tumors account for approximately 50% of anterior mediastinal lesions, while the rest are mostly lymphomas and teratomas.[2]
Although a definitive diagnosis of thymic lesions can be achieved by histologic examination, an appropriate characterization and staging of these lesions may have a significant impact on their management. Positron emission tomography with fluorine-18 fluorodeoxyglucose (F-18 FDG) integrated with multislice computed tomography (PET-CT) combines functional and anatomical information, which provides greater diagnostic accuracy and determination of the extent of neoplastic disease. High resolution magnetic resonante Imaging (MRI) is also very useful in identifying cystic lesions.

Discussion

We present a pictorial review of the main imaging findings by F-18 FDG PET-CT of the thymus in physiological and pathological situations. When considered relevant, MRI images were provided. The various entities were grouped into:

- Age-related changes
- Thymic hyperplasia
- Thymic cysts
- Thymic epithelial tumors
- Thymic lymphoma

Age-related changes
The thymus is a lymphoid organ that plays an essential role in the development of the immune system during childhood and, accordingly, it undergoes dynamic changes with age and disease.[1] In younger patients, it may demonstrate predominantly soft-tissue attenuation, while in older patients, it may be entirely replaced by fatty tissue.
Although there are sporadic cases of physiological thymic uptake in normal adults in F-18 FDG PET-CT studies, thymic uptake is most noted before puberty, which is the point at which the thymus undergoes fatty infiltration and involution.[2,3]
Typically in physiological thymic uptake, the intensity is low. Maximum standardized uptake values (SUVmax) of the normal thymus have ranged approximately between 1.0 and 1.8, although there is some overlap between these values and those of thymic hyperplasia (Fig. 1).[4]

Thymic hyperplasia
There are two histologic types of thymic hyperplasia: true thymic hyperplasia and lymphoid follicular hyperplasia. The nature of the increase in size of the thymus differs between the two types of hyperplasia: in true thymic hyperplasia, the

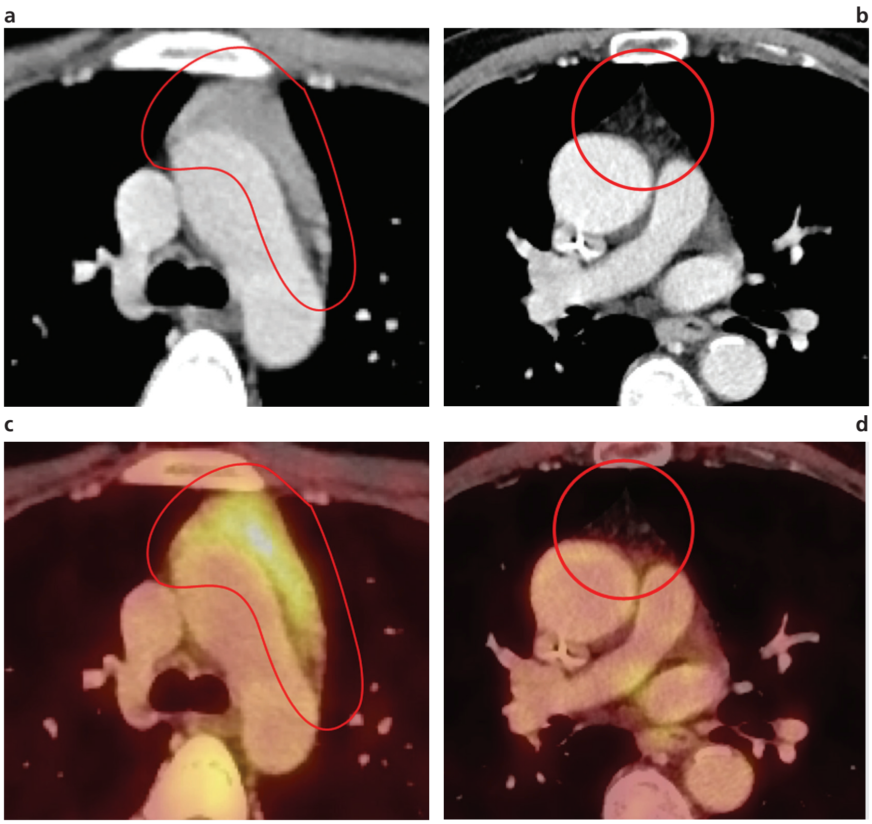

***Fig. 1** Physiological thymus: age-related changes. Axial intravenous (IV) contrast-enhanced CT (A and B) and PT-CT fusion imaging (C and D). Twenty-year old and sixty-five year-old patients (left and right, respectively) with no previous history of chemotherapy. The 20-year-old patient has a quadrilateral thymus with mild 18-FDG uptake, while the 65-year-old patient has a triangular thymus with no significant 18-FDG uptake, demonstrating fatty degeneration typical of the involutional process associated with aging.*

thymic tissue mass is increased, with preservation of the histologic architecture. In lymphoid follicular hyperplasia, enlarged lymphoid germinal centers account for the increased size of the gland. True thymic hyperplasia or rebound thymic hyperplasia is a phenomenon characterized by an increase in the thymus sice after a stressor, such as chemotherapy, radiation, corticosteroid therapy, burns or surgery.[5] Lymphoid follicular hyperplasia is associated with various chronic inflammatory and autoimmune disorders, mainly myasthenia gravis, Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune conditions.[6]

Although the two types of thymic hyperplasia are impossible to differentiate at imaging, thymic hyperplasia can often be distinguished from expansion processes on the basis of certain guiding findings. Thymic hyperplasia usually manifests as a diffuse and symmetric enlargement of the thymus, with smooth contours, interspersed fat and soft-tissue elements and preserved fat cleavage planes (Fig. 2). In contrast, a thymic tumor may demonstrate a focal mass, nodular contours, heterogeneity (representing hemorrhage or necrosis), and/or calcifications.[7] SUVmax values of F18-FDG uptake in thymic hyperplasia range approximately between 2.0 and 2.8.2 Chemical shift MRI can be used. Thus, in thymic hyperplasia, loss of signal intensity can be observed on the out-of-phase images relative to the in-phase images due to the presence of microscopic fat in the hyperplasic thymus (Fig. 3).[8]

Thymic cysts

Thymic cysts are relatively uncommon lesions, with no predominance in any age group. They may be congenital or acquired in origin. Congenital cysts can be found anywhere along the thymopharyngeal duct, while acquired cysts develop after chemotherapy, thoracotomy, or in association with thymic tumors.[9] On computed tomography, these cysts appear as nodular lesions with fluid density, showing thin or imperceptible walls; internal septations can be seen. Occasionally, their walls may slightly enhance with intravenous contrast administration. Their appearance may be less typical when

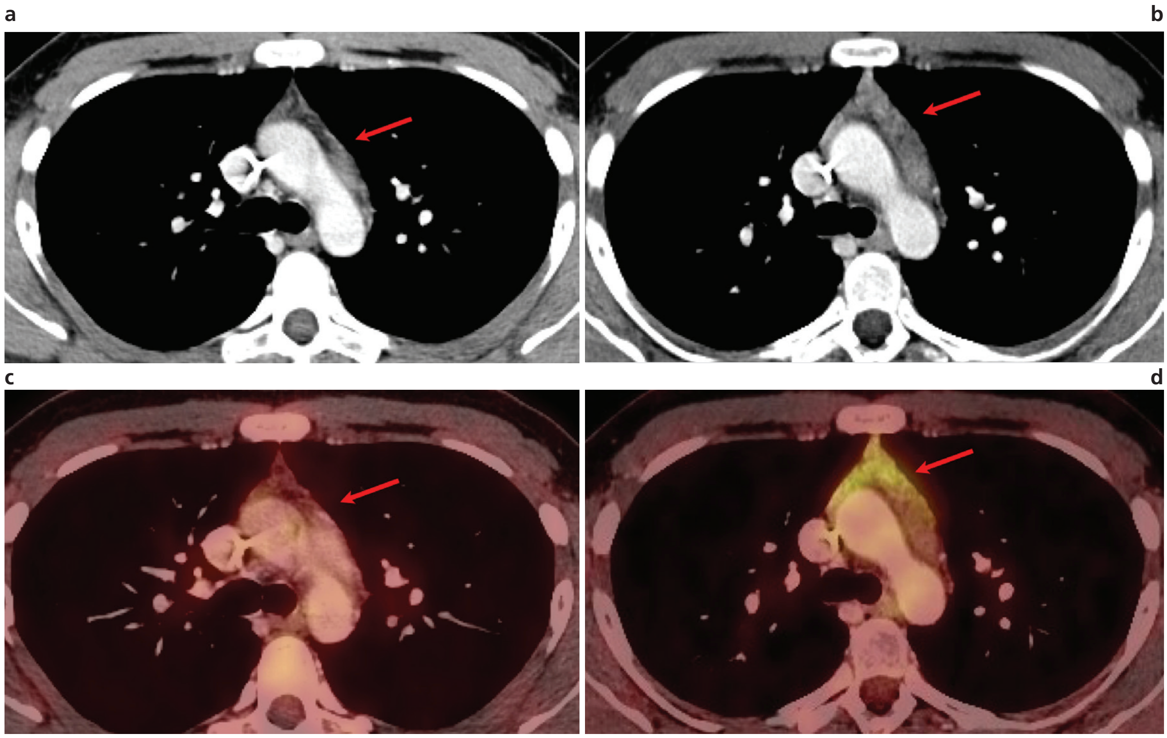

***Fig. 2** Rebound hyperplasia. Axial IV contrast-enhanced CT (A and B) and PET-CT fusion imaging (C and D). Twenty-one year-old male patient who underwent chemotherapy for testicular tumor. Pre- (A and C) and post- (B and D) chemotherapy images revealed a slight enlargement of the thymus and significantly increased F18-FDG uptake (SUVmax: 3.8). The lesion was diagnosed as rebound thymic hyperplasia. The patient continues with no changes after two years of follow-up.*

infection or hemorrhage occur as complications, in which cases they may appear somewhat heterogeneous, requiring differential diagnosis from solid masses. Contrast-enhanced MRI may be useful to distinguish hemorrhagic fluid from soft tissues.[10] On PET-CT examination, these lesions show no F18-FDG uptake (Fig. 4).

Thymic epithelial tumors

Thymic epithelial tumors include thymoma and thymic carcinoma, with these being the predominant tumors of thymic origin. The World Health Organization (WHO) histologic classification divides thymomas into A, AB, B1, B2, B3 or C according to the morphology and degree of atypia of epithelial tumor cells in the order of increasing degree of malignancy.[11] Several staging classifications have been proposed for thymic epithelial tumors, with the Masaoka-Koga Staging System being the most widely used.[12] However, the classification recently proposed by the International Association for the Study of Lung Cancer / International Thymic Malignancy Interest Group (IASLC/ITMIG, appears to be very promising due to its methodological robustness and incorporation into the eighth edition of the American Joint Committee on Cancer (AJCC) staging manual.[13]

Thymoma is the most common anterior mediastinal mass in adults.7 Although these tumors are generally asymptomatic, 20 to 30% of patients may develop symptoms of thoracic compression, myasthenia gravis, pure red cell aplasia or other immune disorders. In particular, the relationship of thymoma with myasthenia gravis is well established: 15% of patients with myasthenia gravis have thymomas.[14]

The role of imaging in thymic epithelial tumors is to identify and accurately stage these lesions, with an emphasis on the detection of signs of advanced disease, such as local invasion, lymphadenopathy and distant metastasis.13 Identification of patients with advanced disease is highly relevant, since preoperative neoadjuvant chemotherapy may be administered to achieve complete surgical resection, improving prognosis in these patients.[15]

On Ct scans, thymomas are generally seen as homogeneous, soft-tissue masses of well-defined borders and a lobulated, round or ovoid morphology. Occasionally, calcifications or low-density components that represent necrosis can be seen (especially in large tumors) (Fig. 5).[16] Up to 5% of patients with invasive thymomas can present with metastases and, 18F-FDG being a whole-body imaging method, most useful for their detection.[17]

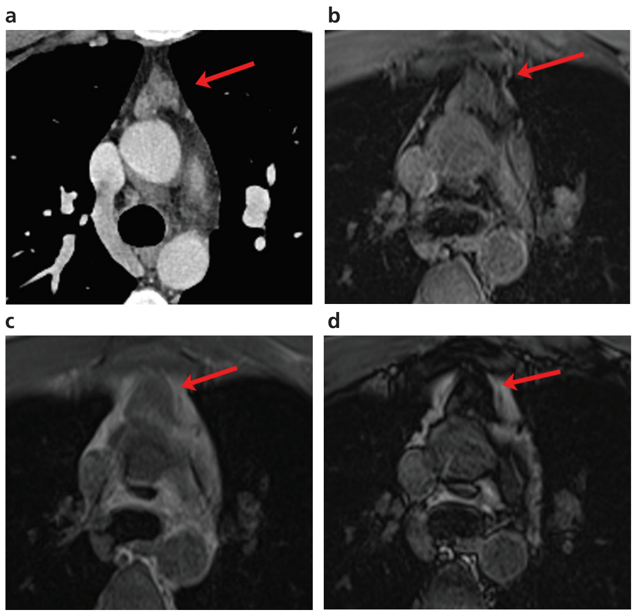

Fig. 3 *Thymic hyperplasia. Axial non-contrast-enhanced CT scan (A) shows a prevascular mediastinal mass with soft-tissue density and nodular morphology, with a slight enhancement after paramagnetic contrast administration on MRI (B). The lesion shows a loss of signal intensity on out-of-phase gradient-echo sequences (C and D).*

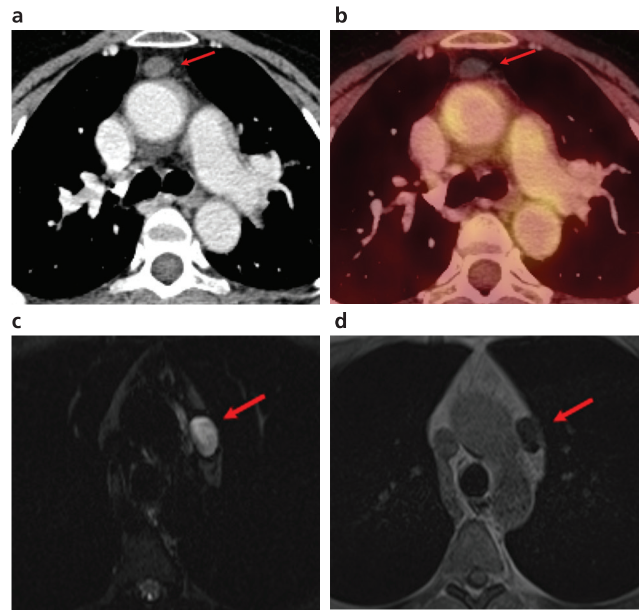

Fig. 4 *Thymic cyst. Axial IV contrast-enhanced CT and PET-CT fusion images (A and B) show a well-circumscribed nodule with fluid density, imperceptible walls, no enhancement with IV contrast and no F18-FDG uptake. Axial images of a chest MRI of a different patient show a nodular mass that appears hyperintense on T2-weighted sequences (C) and hypointense on T1-weighted sequences (D), with a fat cleavage plane with the left lateral wall of the aortic arch, and not deforming the mediastinal contour.*

The ability of 18F-FDG PET-CT to differentiate invasive (high-risk) thymomas from non-invasive (low-risk) thymomas generates controversy because the marked overlap in FDG uptake between invasive and noninvasive thymomas. Nevertheless, there is a relative agreement that invasive thymomas show higher uptake as compared to noninvasive thymomas.[18]

Thymic carcinoma may be difficult to distinguish from a locally advanced thymoma on imaging, but thymic carcinoma tends to be more aggressive, with rapid invasion of adjacent structures. Thymic carcinoma usually lacks a capsule, and lymphadenopathy and distant metastases are suggestive of this diagnosis. On CT, they usually present as heterogeneous, multilobulated masses with areas of necrosis and calcification. They have a high uptake, typically with SUV_{max} greater than 7 (Fig. 6).[6]

Distant metastases are uncommon at the time of presentation of thymic epithelial tumors. The most common metastatic site is the pleura ("drop metastases"), while involvement of the kidney, bone, liver and brain is less frequent.[19]

Lymphoma

Lymphoma is the most common cause of prevascular mediastinal mass in children and young adults.[20] Thymic involvement in lymphoma generally occurs in the setting of widespread disease, but, occasionally, isolated involvement of the thymus may be seen. On imaging, lymphoma can be difficult to distinguish from other thymic masses. On CT scans, it may appear as diffuse thymic enlargement, a single dominant mass or multiple separate masses.[13] The appearance most suggestive of lymphoma is a nodular, asymmetrical enlargement of the thymus. The presence of a mass of these characteristics associated with lymphadenopathy in a young patient is suggestive of the diagnosis. PET-CT shows similar findings, associated with increased SUVmax, usually over 3.4 (Fig. 7). The SUV_{max} value is considered to be predictive of aggressiveness: values over 13 are suggestive of aggressive lymphoma and values less than 6 are suggestive of indolent lymphoma.[21]

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing.

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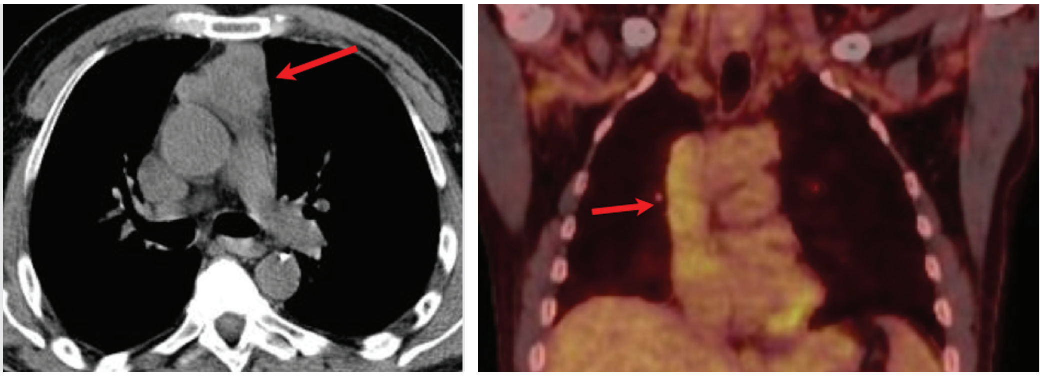

Fig. 5 *Invasive thymoma. Axial images. Fifty-two year-old man. Non-contrast-enhanced CT (A) shows a prevascular mass with loss of fat plane. Coronal PET-CT fusion imaging (B) shows a hypermetabolic mass (SUVmax 4.5) extending through the superior vena cava into the right atrium.*

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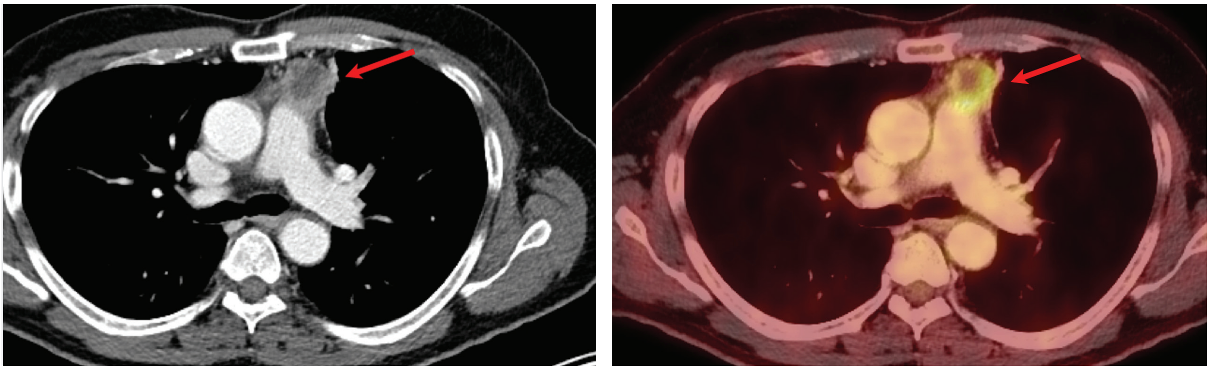

Fig. 6 *Thymic carcinoma. Sixty-six year-old man. Axial contrast-enhanced CT image (A) shows a multilobulated prevascular mass with a solid peripheral contrast-enhancing component and a non-enhancing center compatible with necrosis. No cleavage plane with the pulmonary artery. PET-CT fusion imaging (B) shows high radiotracer uptake in the solid portion of the lesion (SUV_{max}: 17.5).*

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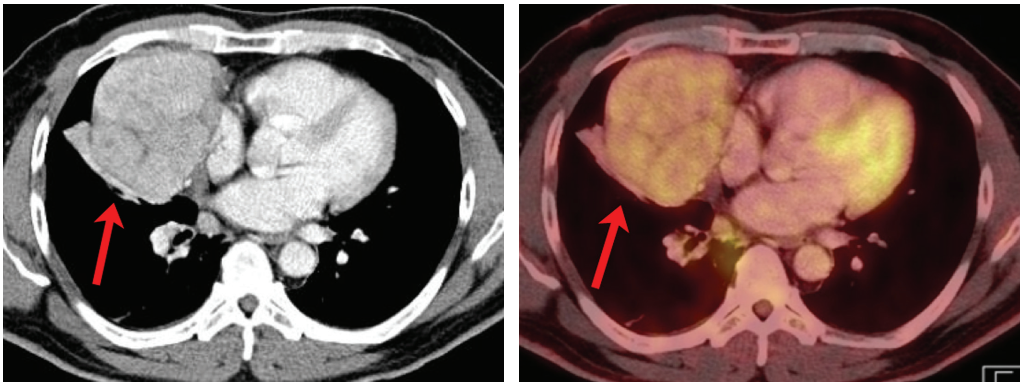

Fig. 7 *Non-Hodgkin lymphoma. Axial images. Prevascular mass with slightly heterogeneous enhancement on IV contrast-enhanced CT (a). PET-CT fusion imaging (B) shows mild hypermetabolism (Suv_{max} 4.2).*

Conflicts of interest

The authors declare no conflicts of interest.

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