Clinical Imaging 38 (2014) 771–784

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

# Diagnostic and functional imaging of thymic and mediastinal involvement in lymphoproliferative disorders

Adriano Massimiliano Priola [a,*], Giorgio Galetto [b], Sandro Massimo Priola [a]

[a] Department of Radiology, San Luigi Gonzaga University Hospital, Orbassano, Torino, Italy
[b] Department of Emergency Medicine, Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

ARTICLE INFO

*Article history:*
Received 13 March 2014
Received in revised form 7 May 2014
Accepted 27 May 2014

*Keywords:*
Thymus
Lymphoma
Computed tomography
Magnetic resonance imaging
$^{18}$F-FDG/PET–CT

ABSTRACT

Lymphoproliferative disorders of the anterior mediastinum may involve the thymus or lymph nodes as part of disseminated disease or as an isolated site. Imaging is crucial in managing patients with mediastinal lymphoma and is employed in pretreatment assessment, midtreatment evaluation of response, posttreatment restaging, and surveillance during follow-up. For decades, computed tomography (CT) has been the standard imaging technique, although in the last years, positron emission tomography (PET)–CT and magnetic resonance imaging (MRI) have been introduced. We discuss the role of different imaging techniques in the assessment of patients with mediastinal lymphoma, focusing on novel aspects of PET–CT and diffusion-weighted/MRI.



## 1. Introduction

Involvement of the anterior mediastinum in lymphoproliferative disorders, namely, lymphomas and leukemias, usually occurs in the setting of generalized disease, although isolated thymic involvement is not uncommon. Lymphoma is the most common cause of anterior mediastinal mass in children, representing 50% of all mediastinal tumors, and the second most common cause in adults [1]. In adulthood, lymphoma accounts for nearly 20% of anterior mediastinal masses, a lower percentage compared to thymoma that usually affects older patients [2]. In 5% of cases, the anterior mediastinum is the only site of disease (primary mediastinal lymphoma); in these cases, lymphoma may manifest as isolated thymic involvement, that usually appears as a diffuse thymic enlargement, as isolated nodal involvement, with single or multiple masses, or as a combination of both [3]. Hodgkin's lymphoma (HL) accounts for the majority of primary mediastinal lymphomas. Nodular sclerosis is the most common histological subtype that affects the thymus and usually occurs in young female adults. Conversely, thymic involvement is much less common in non-HL (NHL) that tends to affect lymph nodes of the anterior mediastinum rather than the thymus [4–6]. Furthermore, up to 70% of patients with systemic disease and mediastinal involvement have HL and 15%–25% have NHL [2]. In NHL, the two most common forms are lymphoblastic lymphoma and diffuse large B-cell lymphoma that usually appear as huge mediastinal masses and tend to have local aggressiveness and distant spread (hematic and non-contiguous lymph node spread). The former mainly affects children and adolescents; the latter usually occurs in young to middle-aged adults with a mean age of 30 years [4,5]. Lymphoblastic lymphoma has a predilection for rapid dissemination and the tumor spreads to extrathoracic lymph nodes, bone marrow, central nervous system, and gonads in extensive disease [3].

Most patients with HL are asymptomatic, and systemic symptoms that identify category B of Ann-Arbor staging system (Table 1) are found in only 20%–30% of cases at presentation. However, local symptoms may also occur in patients with bulky masses as chest pain, cough, dyspnea, and dysphagia [2,3]. Conversely, nearly all patients with NHL typically present with local symptoms, such as respiratory distress and superior vena cava syndrome, because NHLs commonly appear as large anterior mediastinal masses that compress the airway and cardiovascular structures [2,3].

The differential diagnosis of primary mediastinal lymphoma includes thymoma, thymic malignancies (carcinoma and carcinoid), benign and malignant germ cell neoplasms, and lymph node metastases [3,7–9]. The correct diagnosis based solely on diagnostic imaging may be challenging, particularly in cases of isolated mediastinal involvement from lymphoma [2]. Furthermore, the distinction between lymphomatous involvement of the thymus and a prominent but normal thymus in pediatric and adolescent patients or rebound thymic hyperplasia (RTH) after treatment can pose considerable diagnostic difficulties [8].

* Corresponding author. Department of Diagnostic and Interventional Radiology, University of Turin, San Luigi Gonzaga Hospital, Regione Gonzole 10, 10043 Orbassano, Torino, Italy. Tel.: +39 011 9026 785; fax: +39 011 6705 463.
*E-mail address:* adriano.priola@inwind.it (A.M. Priola).

http://dx.doi.org/10.1016/j.clinimag.2014.05.012
0899-7071/

**Table 1**
Ann Arbor staging classification and Cotswold modification for HL and NHL

| Stage | Area of involvement |
|---|---|
| I | Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) |
| II | Involvement of two or more lymph node regions or lymphatic structures (e.g., spleen, thymus, Waldeyer's ring) on the same side of the diaphragm alone (II), or localized involvement of a contiguous extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE) |
| III | Involvement of lymph node regions on both sides of the diaphragm (III), which may also include involvement of the spleen (IIIS) or localized involvement of a contiguous extralymphatic organ or site (IIIE) or both (IIIES) |
| IV | Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues (beyond those designated as "E"), with or without associated lymphatic involvement |

| Additional qualifiers | |
|---|---|
| Systemic symptoms[a] (for all stages) | A: Absence<br>B: Presence |
| E (for stages I–III) | Involvement of a single, extranodal site contiguous or proximal to known nodal site |
| S (for stage III) | Involvement of the spleen |

Cotswold modification

- Bulky disease (massive mediastinal disease) indicated as "X" is defined as a thoracic ratio of maximum transverse mass diameter ≥33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disk level or maximal diameter >10 mm of a nodal mass.
- The number of anatomic regions involved is indicated by a subscript (e.g., $II_3$).
- Stage III is divided into the following: $III_{(1)}$, with or without splenic, hilar, celiac, or portal nodes; $III_{(2)}$, with para-aortic, iliac or mesenteric nodes.
- Staging is identified as clinical stage or pathologic stage obtained through biopsy and denoted by a subscript (e.g., M=bone marrow).

[a] Unexplained fever ≥38°C, weight loss >10% of body weight during the previous six months, unexplained drenching night sweats, itching.

At last, another key issue in mediastinal lymphoma is the assessment of early treatment response and the need for a reliable cancer imaging biomarker that is able to monitor and predict the response of tumor to treatments in order to reduce the risk of treatment failure, avoid unnecessary treatment toxicity, and increase the chance of long-term survival [10].

On these bases, the aims of this review are to highlight the role of diagnostic and functional imaging in patients with mediastinal and thymic lymphoma and to discuss the role of various imaging techniques for detection, staging, and follow-up of lymphoproliferative disorders, including novel aspects for monitoring and predicting treatment response (Table 2).

## 2. Conventional radiography

Chest radiograph (CR) is the first step in the evaluation of patients with signs and symptoms suggestive for lymphoproliferative disorder [11]. Moreover, since many patients with HL are asymptomatic, mediastinal lymphoma may be incidentally discovered at CR [2,8,9]. Even in young patients, both frontal and lateral CR should be performed because small anterior mediastinal lymphadenopathies that do not distort the mediastinal contours may go undetected on the unique frontal view [11,12]. On frontal CR, small lymphomas may obliterate the anterior junction line, may solely appear as focal or diffuse thickening of the anterior junction line, or may determinate an abnormal mediastinal contour [7,12]. Conversely, on lateral view, especially in cases of normal frontal CR, the abnormality, although small, may manifest as a vague increased opacity in the retrosternal space [12]. CR may help detect relatively large lymphomas, and as many as 70% of them are identified on frontal CR [13]. When large, on frontal CR, lymphomas typically appear as lobulated and well-marginated smooth masses that extend more frequently to both sides of the mediastinum, whereas unilateral tumor growth is less frequent and usually seen in thymoma [2,7,14] (Fig. 1a, c). The "hilum overlay sign" is appreciable when the normal hilar structures project through the mass, such that the mass can be understood as being anterior if posterior mediastinal lines are preserved [12] (Fig. 1a, d). Furthermore, on frontal CR, lymphomas that extend to the inferior anterior mediastinum and thus overlie the cardiac silhouette may obliterate partially or completely one or both sides (right and left) of the heart (Fig. 1a, e). On lateral radiograph, large lymphomas usually manifest as sharply marginated retrosternal areas of increased opacity with smooth or lobulated borders or as areas of subtle increased opacity in the retrosternal clear space [7,9] (Fig. 1b). At last, occasionally, CR may detect pleural effusion and lung involvement that can occur more frequently in NHL.

## 3. Computed tomography

Computed tomography (CT) is currently considered the cross-sectional imaging modality of choice in patients which present abnormalities at CR or signs and symptoms suggestive for

**Table 2**
Role of imaging techniques in the management of patients with mediastinal lymphoma

| Technique | Identification | Staging | Treatment response | | Follow-up | Diagnosis[a] |
|---|---|---|---|---|---|---|
| | | | Early[b] | Post | | |
| Conventional radiography | Y | N | N | N | N | N |
| CT | Y | Y | N | Y | Y | Y |
| $^{18}$F-FDG/PET–CT | N | Y | Y | Y | Y | N |
| Magnetic resonance | N | Y | Y[c] | Y[c] | Y | N |
| US | Y | N | N | N | N | Y |

Y=yes; N=no.
[a] Histological diagnosis obtained through core needle biopsy guided by imaging.
[b] In the setting of clinical trials.
[c] With the use of diffusion-weighted imaging.