



Mediastinal lymphomas – differential diagnosis

Limfomi medijastinuma – diferencijalna dijagnoza

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Introduction

The mediastinum is an extrapleural space between the two pleural cavities. Anatomically the mediastinum is divided into the anterior – prevascular, middle – vascular and posterior – paravertebral sulcus – costovertebral space¹. The mediastinal space is divided into the four parts, according to clinical-radiological aspect of localization of the pathological lesions with respect to diagnostic and therapeutical approach² (Figure 1): 1) Superior mediastinum – retrosternal

granulomatous diseases (tuberculosis, sarcoidosis), metastatic carcinoma, pleuropericardial cysts, tumors of the heart, lymphangiomas, neuroenteric cysts and gastroenteric cysts, cysts of ductus thoracicus and other rare cysts; 4) Posterior mediastinum – neurogenic tumors, aortic aneurysms, bronchogenic and enterogenic cysts, lymphatic lesions, fibromas, lipomas and liposarcomas.

Mediastinal lesions are rare and account for 1% of all tumors. They appear in all age groups, having the highest incidence in the third and fourth decade of life, and they have even sex distribution. Approximately 60% of lesions are benign, while approximately 40% are malignant in their nature.

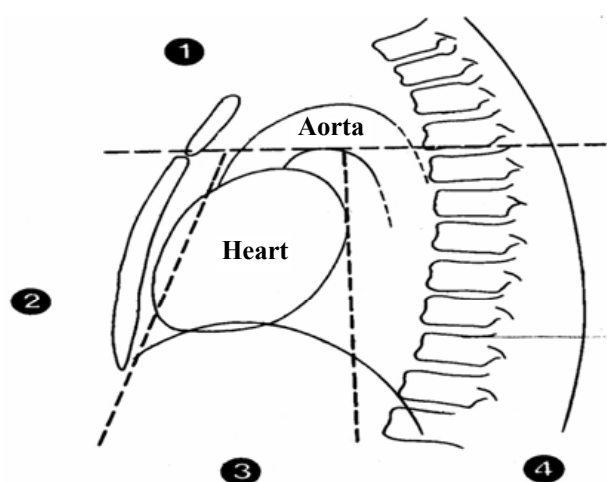


Fig. 1 – Clinical – radiological division of the mediastinum

1 – Superior mediastinum; 2 – Anterior mediastinum;
3 – Middle mediastinum; 4 – Posterior mediastinum

thyroid, aortic aneurysm, thymic tumor; 2) Anterior mediastinum – thymic tumors, lymphomas, teratomas, pleuropericardial cysts, dermoid cysts, thymic cysts; 3) Middle mediastinum – lymphonodular masses, bronchogenic cysts,

Diagnostic methods in mediastinal tumors

When a tumor mass is evident in the mediastinum, there are a number of both noninvasive and invasive methods for establishing adequate diagnosis^{3–5}.

Noninvasive diagnostic methods in mediastinal tumors: radiological – standard and profile radiography and tomography; esophagography, radioisotope imaging, angiological methods, computerized tomography (CT) of the thorax, magnetic resonance (MR) and positron emission tomography (PET); ultrasonography (ECHO) – transesophageal ECHO cardiography, ECHO of the heart and large blood vessels, ECHO of the neck (cervical blood vessels, thyroid gland), abdominal ECHO; mediastinal tumor markers; cytological and bacteriological sputum analyses; standard laboratory tests.

Invasive diagnostic methods in mediastinal tumors: endoscopic – bronchoscopy, esophagoscopy, surgical endoscopic methods with biopsy – anterior and parasternal mediastinoscopy, video-assisted thoracoscopic surgery, VATS anterior video-mediastinoscopy, puncture needle biopsies –

transthoracic, transbronchial, surgical biopsies – parasternal mediastinotomy and cervical lymph node biopsy, exploratory thoracotomy and sternotomy – posterolateral or medial sternotomy

Careful clinical examination and recognition of signs and symptoms that may be a part of clinical manifestations of the mediastinal process (syndrome of compression of the superior *vena cava*, cervical adenopathy, neurological events, atrophy of the arm muscles, eyelid ptosis, anisocoria, dysphagia, dyspnea, stridor, etc.) is important for planning of a diagnostic procedure. A large proportion of mediastinal tumors and masses – 40% produce no symptoms and are found incidentally during chest radiograph or imaging studies of the thorax performed for other reasons, while 97% can be detected on postero-anterior (PA) and lateral chest radiographs^{1,6}. The most common symptoms appearing in approximately one half of all patients are caused by compression of the surrounding structures by the tumors, dislocation, occlusion and fixation of the vital structures. Thoracic pain is a frequent symptom, while the majority of the patients complain of the respiratory disorders (cough and dyspnea) caused by extramural compression or invasion of the airway walls. Other frequent symptoms include dysphagia (due to esophageal dislocation), syndrome of the superior *vena cava* obstruction, pleural pain and pain in the shoulder, paralysis of the recurrent laryngeal nerve and Horner syndrome, phrenic nerve paralysis, onset of pleural effusion, back pain, paraplegia, etc.^{7,8}.

Clinical characteristics of mediastinal tumors

Mediastinal lymphomas develop as primary neoplasms of the mediastinal and thymic lymph nodes or they affect these organs in the course of systemic dissemination of the lymphoma originating from other sites in the organism¹. These are most frequently primary mediastinal tumors, most of them being localized in the anterior mediastinum, although they may also appear as a mass in the middle mediastinum. Mediastinal lymphomas may develop in all age groups; however they are most common in the third and fourth decades of life. According to the World Health Organization (WHO) classification, all lymphoma subtypes may develop in the mediastinum. The most common is classical Hodgkin's lymphoma (cHL) of the nodular sclerosis type⁹. Non-Hodgkin's lymphomas (NHL) are less frequent, with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma with sclerosis (PMBL) and T-lymphoblast lymphoma being the most common. Symptoms of the mediastinal lymphoma are similar to those evidenced in other mediastinal tumors but, as opposed to other tumors, lymphomas are accompanied by numerous systemic complaints such as weakness, malaise, fever, elevated body temperature, loss of weight and enhanced overnight sweating. The above-described diagnostic methods are applied in diagnosis of the mediastinal lymphoma. Determination of tumor mass size, i.e. its bulkiness, expressed as thoracomediastinal index (TM) is of particular importance for staging of the disease in these patients¹⁰. The presence of the mediastinal

adenopathy greater than 1/3 of the horizontal TM (33% of the thoracic aperture) and/or presence of the nodal mass of maximal dimension greater than 7 cm indicate a bulky tumor mass. Rather large bulky tumor mass occupies more than 45% of the thoracic aperture¹¹ (Figure 2).



Fig. 2 – Radiographic verification of bulky mediastinal lymphoma

As for pulmonary parenchyma infiltration in *de novo* Hodgkin's lymphoma (HL), the pulmonary parenchyma is almost never affected without affection of the mediastinal lymph nodes and, almost always, the ipsilateral hilar lymph nodes^{6,12}. The situation is different in NHL, where pulmonary lesions may also be the only manifestation of intrathoracic disease in the absence of lymphadenopathy of the upper mediastinum or hilar lymphadenopathy¹².

Computerized tomography does not distinguish benign from the malignant lesions. However, application of intravenous contrast enables differentiation between vascular and other pathological changes and determination of the relation of a lesion to the surrounding blood vessels. Computerized tomography visualizes infiltration of the subpectoral region and axillae, which do not necessarily need to be palpable (which is important for planning of the therapy)³.

The differential diagnosis of mediastinal tumors

Hodgkin lymphoma, nodular sclerosis subtype

Hodgkin lymphoma, nodular sclerosis is the most common primary malignant mediastinal neoplasm. As is the case with PMBL, it is most commonly diagnosed in young women in the third and fourth decades of life¹³. It is localized in the superior mediastinum spreading to the cervical lymph nodes, or it may ingrow into the surrounding intrathoracic organs. More than 90% of mediastinal HL belong to the nodular sclerosis subtype. Histologically, there is a characteristic nodular growth pattern with wide bands of the hyalinized, hypocellular connective tissue which surrounds tumor nodules. The tumor tissue is made of a variable number (usually < 5% tumor mass) of neoplastic, mononuclear Hodgkin cells, polynuclear Reed-Sternberg (RS) cells and characteristic lacunar cells. The classical immunophenotype is CD45-, CD20-, EMA-, CD30+, CD15+, LMP+^{14,15}. At

presentation, the bulky form of the disease is found in 40% of all patients and the disease is manifested by numerous systemic complaints. Planning of suitable therapy is based on the international prognostic score (IPS), which considers the following prognostic parameters as unfavorable: male sex, age above 45, hypoalbuminemia (less than 4 g/dL), anemia (Hb below 10.5 g/dL), leukocytosis above 16 000, lymphocytopenia (600/mm³ or 8%) and clinical stage IV^{16,17}.

Primary mediastinal B-cell lymphoma with sclerosis

Primary mediastinal B lymphoma with sclerosis (PMBL) is a subtype of the DBCL, which is, based on its frequency, the second most frequent mediastinal neoplasm^{18,19}. The tumor is frequent in women in the third and fourth decades of their life, while it is rare in men in the fifth decade^{20,21}. It is a special type of the diffuse large cell NHL originating from the thymic B-lymphocytes and it is characterized by particular clinical, immunophenotypic and genetic properties^{22,23}. From both histological and prognostic points of view, 3 subgroups of DBCL may be distinguished (originating from the germinal center, activated B-cells and PMBL)¹³. Histologically, PMBL is characterized by diffuse proliferation of the large lymphoid cells accompanied by prominent sclerosis; tumor cells are large with prominently pale cytoplasm with multinuclear cells being also occasionally present which makes the differential diagnosis between HL impossible in the absence of detailed immunohistochemical tests²⁴. Immunophenotypically, they are characterized by positivity for CD45, CD20, CD79 α however also by negativity for CD3, CD5, CD10, CD21 and HLA DR I/II²⁵. The tumor cells express B-cell antigens; however, as opposed to other large cell lymphomas originating from B-lymphocytes, they do not express HLA antigens and immunoglobulins²⁶. In the majority of patients, the tumor is manifested as a large intrathoracic mass located in the anterior mediastinum. Symptoms include dyspnea, cough, *superior vena cava* syndrome, pleural and/or pericardial effusion^{20,21}. In most patients evidence of the disease is limited to the chest. However, in 25% of patients dissemination occurs in the course of diseases progress, usually to the extranodal locations, such as kidneys, adrenal glands, liver, skin, brain and digestive tract. Prognosis is less favorable in patients

with the affected intrathoracic organs in comparison with those in whom the disease is localized only within the mediastinum. Where there is involvement of the extrathoracic organs, particularly sub diaphragmatic ones, prognosis is particularly poor^{18,20}.

Precursor T-cell lymphoblast lymphoma/leukemia

Precursor T-cell lymphoblast lymphoma/leukemia is a neoplasm originating from the lymphoblasts determined for T-cell differentiation and it involves bone marrow, blood and it is occasionally primarily manifested as lymph node tumor or it may be located extranodally. As opposed to acute lymphoblast leukemia, since they biologically represent the same entity, diagnosis of precursor T-lymphoblast lymphoma is usually made in patients having large nodal/extranodal tumor mass and less than 25% of the lymphoblasts in the bone marrow. Precursor T-cell lymphoblast lymphoma accounts for approximately 85–90% of all lymphoblast lymphomas^{14,15}. The disease is most frequently evidenced in men in the second and third decades of their life²⁷. The tumor is manifested in 50% of the patients as a fast-growing, large mediastinal mass which is frequently accompanied by the development of pleural and/or pericardial effusions. High leukocytosis with true picture of leukemia is present in individual cases. In addition to the mediastinal and bone marrow changes, peripheral lymphadenopathy or skin, liver, spleen Waldeyer ring, central nervous system and gonadal involvement may be present as well. Microscopically, the tumor is composed of moderately-sized cells with sparse cytoplasm, round or notched nuclei and indistinct nucleolus. The mitotic index is high with frequent “starry sky” effect. Differentiation from other mediastinal lymphomas is based on immunohistochemical analyses. All cases are TdT and CD3. Most cases also express CD1a, CD2, CD7 and CD43, while staining for CD4 and CD8 is variable^{14,15}.

Conclusion

It is important to emphasize the accurate diagnosis of mediastinal lymphomas, by adequate patohistological and immunohistochemical analysis which can provide appropriate therapy.

R E F E R E N C E S

1. *Bartlett NL, Wagner ND.* Lymphoma of the mediastinum. In: *Pearson FG, Cooper JD, Deslauriers J, Ginsberg RJ, Hiebert CA, Patterson G,* et al, editors. *Thoracic surgery.* Section VII. Mediastinum. 2nd ed. New York: Churchill Livingstone; 2002. p. 1724–31.
2. *Skarin AT.* Atlas of Diagnostic Oncology. 2nd ed. London: Mosby-Year Book Europe; 1996.
3. *Castellino RA, Hilton S, O'Brien JP, Portlock CS.* Non-Hodgkin lymphoma: contribution of chest CT in the initial staging evaluation. *Radiology* 1996; 199(1): 129–32.
4. *Carlsen SE, Bergin CJ, Hoppe RT.* MR imaging to detect chest wall and pleural involvement in patients with lymphoma: effect on radiation therapy planning. *AJR Am J Roentgenol* 1993; 160(6): 1191–5.
5. *Tesoro-Tess JD, Balzarini L, Ceglia E, Pettilo R, Santoro A, Musumeci R.* Magnetic resonance imaging in the initial staging of Hodgkin's disease and non-Hodgkin lymphoma. *Eur J Radiol* 1991; 12(2): 81–90.
6. *Yoneda KY, Morissey BM, Shelton DK.* Mediastinal tumors – a diagnostic approach business briefing: US Respiratory Care. Available from: <http://www.touchrespiratorydisease.com/mediastinal-tumors-diagnostic-approach-a766-1.html>
7. *Mihaljević B, Sretenović M, Jancić-Nedeljkov R, Petrović M.* Acute megakaryoblastic leukaemia with mediastinal tumor. *Haematologia (Budap)* 1996; 27(3): 155–8.
8. *Mihaljević B, Nedeljkov-Jancić R, Cemerikić-Martinović V, Babić D, Colović M.* Ki-67 proliferative marker in lymph node aspirates

- of patients with non-Hodgkin's lymphoma. *Med Oncol* 2006; 23(1): 83–89.
9. Jaffe ES, Muller-Hermelink K. *Hodgkin's Disease*. In: Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM, editors. *Hodgkin's disease*. Philadelphia: Lippincot Williams & Wilkens; 1999. p. 181.
 10. Bartlett NL, Rosenberg SA, Hoppe RT, Hancock SL, Horning SJ. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol* 1995; 13(5): 1080–8.
 11. Glimelius I, Molin D, Amini RM, Gustavsson A, Glimelius B, Enblad G. Bulky disease is the most important prognostic factor in Hodgkin lymphoma stage IIB. *Eur J Haematol* 2003; 71(5): 327–33.
 12. Mentzer SJ, Reilly JJ, Skarin AT, Sugarbaker DJ. Patterns of lung involvement by malignant lymphoma. *Surgery* 1993; 113(5): 507–14.
 13. Staudt LM, Dave S. The biology of human lymphoid malignancies revealed by gene expression profiling. *Adv Immunol* 2005; 87: 163–208.
 14. Jaffe ES, Harris NL, Stein H, Vardiman JW. Pathology and genetics. Tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours. Lyon: IARC Press; 2001.
 15. Gatter K, Delsol G. Hodgkin's Lymphoma. In: Gatter K, Delsol G, editors. *Atlas: the diagnosis of lymphoproliferative diseases*. Oxford: Oxford University Press Inc; 2002. p. 59–63.
 16. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 1998; 339(21): 1506–14.
 17. Jaković LR, Mihaljević BS, Jovanović MD, Bogdanović AD, Martinić VM, Kravić TK, et al. The expression of Ki-67 and Bcl-2 in Hodgkin's lymphoma: correlation with the International Prognostic Score and bulky disease: a study by the Serbian Lymphoma Study Group (SLG). *Med Oncol* 2007; 24(1): 45–53.
 18. Menestrina F, Chilosi M, Bonetti F, Lestani M, Scarpa A, Novelli P, et al. Mediastinal large-cell lymphoma of B-type, with sclerosis: histopathological and immunohistochemical study of eight cases. *Histopathology* 1986; 10(6): 589–600.
 19. Lichtenstein AK, Levine A, Taylor CR, Boswell W, Rossman S, Feinstein DI, et al. Primary mediastinal lymphoma in adults. *Am J Med* 1980; 68(4): 509–14.
 20. Kirn D, Mauch P, Shaffer K, Pinkus G, Shipp MA, Kaplan WD, et al. Large-cell and immunoblastic lymphoma of the mediastinum: prognostic features and treatment outcome in 57 patients. *J Clin Oncol* 1993; 11(7): 1336–43.
 21. Lazzarino M, Orlandi E, Paulli M, Sträter J, Klersy C, Gianelli U, et al. Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell lymphoma: a multicenter study of 106 patients. *J Clin Oncol* 1997; 15(4): 1646–53.
 22. Addis BJ, Isaacson PG. Large cell lymphoma of the mediastinum: a B-cell tumour of probable thymic origin. *Histopathology* 1986; 10(4): 379–90.
 23. Isaacson PG, Norton AJ, Addis BJ. The human thymus contains a novel population of B lymphocytes. *Lancet* 1987; 2(8574): 1488–91.
 24. van Besien K, Kelta M, Bahaguna P. Primary mediastinal B-cell lymphoma: a review of pathology and management. *J Clin Oncol* 2001; 19(6): 1855–64.
 25. Tsang P, Cesarman E, Chadburn A, Liu YF, Knowles DM. Molecular characterization of primary mediastinal B cell lymphoma. *Am J Pathol* 1996; 148(6): 2017–25.
 26. Pileri SA, Gaidano G, Zinzani PL, Falini B, Gaulard P, Zucca E, et al. Primary mediastinal B-cell lymphoma: high frequency of BCL-6 mutations and consistent expression of the transcription factors OCT-2, BOB.1, and PU.1 in the absence of immunoglobulins. *Am J Pathol* 2003; 162(1): 243–53.
 27. Warnke RA, Weiss LM, Chan JKC, Cleary ML, Dorfman RF. *Tumors of the lymph nodes and spleen*. Washington: Armed Forces Institute of Pathology; 1994.

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