The Atypical Onset with Pleural Effusion of an Indolent Lymphoma
Case report and review of literature

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The goal of pleural fluid assessment is to establish with certainty its etiology and major challenge is the etiologic diagnosis precocity. Pleural effusion as the first and the only event in the onset of non-Hodgkin lymphoma is atypically in the absence of other signs and symptoms. Follicular lymphoma (FL) also called indolent lymphoma the most frequent is a low-grade non-Hodgkin's lymphoma (NHL). In patients with indolent lymphoma affecting the pleura and pericardium is atypical and appears only in aggressive forms, so the onset with pleural effusion is unusual. Serous effusions may occur from onset or during evolution of various subtypes of T cell originated lymphomas or high-grade B cell lymphomas. Primary pleural lymphomas (PPL) have been described at patients with human immunodeficiency virus infection; tuberculosis complicated with chronic pyothorax or after exposure to asbestos. Compared to other similar cases previously reported in the medical literature, the novelty of this case is the atypical onset of low grade of indolent B-cells non-Hodgkin with primary pleural effusion in the absence of personal history as well as of another clinical, laboratory and pleural changes.

Keywords: primary pleural effusion, thoracoscopy, non-Hodgkin lymphoma, immunohistochemistry, metabolic remission

The detection of a pleural effusion by clinical or radiological examination reveals a deviation from the normal physiological state that creates an imbalance between the formation and removal of pleural fluid [1- 3]. Besides establishing with certainty, the etiology of the pleural effusion, in the current era of medicine, another major challenge is the etiologic diagnosis precocity, because it is demonstrated that an early diagnosis ensures increased treatment efficiency and even healing of diseases considered incurable in the past.

We report a case of pleural effusion (PE) which, has proved to be an expression of the onset of indolent non-Hodgkin's lymphoma (NHL) to a patient without significant personal history, where early diagnosis and specific treatment resulted in complete metabolic remission proven by positron emission computed tomography (PET).

Experimental part

We present the case of a 53-year-old Romanian man worker on a civil construction site, smoker, without a significant pathological history, which at anamnesis reports the appearance in April 2018, in full health, of symptoms characterized by altered general condition, unexplained fatigability, fever, dry cough, chest pain, and dyspnoea.

Computer tomography showed absence of lymph nodes in mediastinal floors and axillary; important pleural collection in a large amount that seems to collapse the lower and middle lobe towards the hill with appearance of consolidation area and a positive air bronchogram that raises suspicion of pneumopathy or pneumonic infiltration; the absence of abdominal lymph nodes in the elective sites; intercavoaortically nodular appearance, 3 cm in size, raising suspicion of adenopathy or lymphoma tissue; absence of organomegaly (Figure 1).

Following this diagnosis, in May 2018, the patient is hospitalized in the Thoracic Surgery Clinic with the

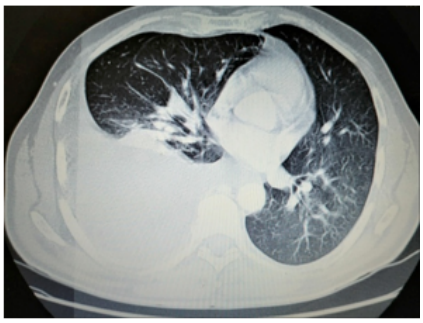

Fig. 1. CT image performed prior to thoracoscopy highlighting: assive right pleural effusion with displacement of the mediastinum, the collapse of the lung in the hillum and, mediastinal lymph nodes absence

symptoms described above slightly relieved but persistent and with signs of important pleural effusion at level of right hemithorax. During hospitalization, for the etiologic diagnosis of pleural effusion thoracentesis was practiced and a serum-citrin fluid was extracted which did not show up at the laboratory test significant changes.

By thoracoscopy, pleural fragments were harvested, and the histopathological examination revealed malignant lymphoid tumour proliferation, vaguely nodular and diffuse, consisting predominantly of small cells with cleaved nucleus; isolated large non-cleaved centroblastic cells (< 15/HPF).

The immunohistochemically examination revealed that tumour proliferation is with B cell, positive diffuse for CD20, with centro-follicular origin, BCL6 positive, poorly positive focal CD10 with a reduced Ki67 proliferation index (-15%); the staining for CD21 revealed follicular dendritic network scrap in nodular areas and tumour proliferation was negative for CD3. The histopathological and immunohistochemically aspect pleaded for appearance of 1-2 grade non-Hodgkin's malignant lymphoma with follicular B cell. Subsequent, the patient is referred to the

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Haematology Clinic for specialized treatment.

At the time of admission, the patient accused only a slight fatigue and the objective examination was found to be relatively good overall condition; without fever or palpable superficial lymph nodes; slight decreased expansion of ipsilateral chest wall, bronchovesicular breath sound absent, dullness and absent fremitus in the lower half of the right chest; liver and spleen with normal size. The blood showed increase of ESR, LDH and alkaline phosphatase and decrease of serum iron. The treatment was performed with the R-CHOP regimen.

Subsequently, positron emission computed tomography was performed using as metabolic tracer fluoro-deoxy-glucose (FDG) and revealed the absence of cervical and supraclavicular lymph nodes, absence of morphological changes at the cranio-cervical level; absence of axillary, mediastinal-hilar lymph nodes or pulmonary nodules; absence of pleural and pericardial fluid; absence of lombo-aortic, iliac or inguinal lymph nodes; absence of changes in the abdominal-pelvic organs, absence of intraabdominal fluid and without suspicious bone lesions. The score Deauville is 1 in 5 five-point scale, that pleaded for complete metabolic remission (Figure 2).

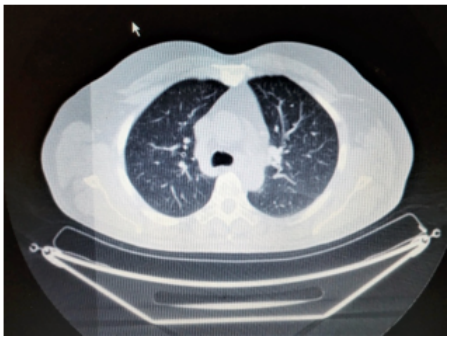

Fig. 2. Image obtained by PET after treatment showing the absence of pleural effusion and mediastinal adenopathies.

Results and discussion

Primary pleural NHL is an extremely rare condition and has a very low frequency, representing approximately 2.4% of the total thoracic wall tumours. On the other hand, non-Hodgkin's systemic lymphoma develops pleural effusion in about 16% of cases [4-6].

In addition, pleural effusion as the first and the only event in the onset of non-Hodgkin lymphoma is atypically if there are no other clinical signs like lymph nodes or organomegaly [7].

In the study conducted in 1998 by Elis et al on 19 patients with non-Hodgkin's malignant lymphoma and PE showed that in NHL, the main mechanism of the PE, is direct infiltration of the pleura [8]. The presence of pleural tumour is rare and usually appears later, this statement being supported by study of Burgener and Hamlin in which the pleural plaques was reported in 4% of patients [9].

Primary pleural lymphomas (PPL) have been described in the literature at cases with human immunodeficiency virus (HIV1) infection also called the body cavity-based lymphoma as well as like pyothorax-associated lymphoma (PAL) in patients with tuberculosis because of chronic pleural inflammation is usually a diffuse large B-cell lymphoma or immunoblastic type associated with presence of Epstein-Barr virus [10-13]. However, in immunocompetent patient without a chronic pyothorax, primary pleural NHL occurs very seldom [14, 15]. Radiological aspect in primary effusion lymphoma (PEL) is pleural effusion without tumour mass whereas in PAL it can be noted homogeneous or inhomogeneous pleural thickening with or without bone destruction [16].

In patients with HIV-associated NHL, PEL appearing only at approximately 4% of the total [17]. Kano & colab. in 1999; Keung & colab. in 1996 have reported two cases of high grade B cell primary pleural NHL in an immunocompetent patient without a history of chronic pyothorax [18, 19]. In 2013 Ru et al. reported another case of primary malignant lymphoma arising in the pleura in a patient with no history of HIV infection or pyothorax, manifested as an uneven pleural neoplasm with varying degrees of mass effect causing dyspnea with histopathological and immunohistochemically with features of small B-cell lymphoma [20].

Tazuko et al have reported in 1994 three cases of pyothorax associated high grade NHL of B cell origin in patients with a previous artificial pneumothorax to treat tuberculosis or with persistent chronic tuberculous pyothorax [21]. In 2003 Ahmad et al, described two cases of nonpyothorax associated low grade NHL, one with exposure to asbestos and other with personal history of tuberculosis. The patients with chronic inflammation secondary to Helicobacter pylori infection have developed gastric lymphoma are another example [13]. Otherwise Jacobson et al reported in 1990 patients with NHL after exposure to asbestos [22]. Thereby, presence of PPL requires differential diagnosis with pleural mesothelioma [20].

Celikoglu et al, in a study conducted in 1992 on 19 patients have highlighted that PE is the predominant sign of a non-Hodgkin's malignant lymphomas onset due to direct affect of the pleura [23]. Jiang et al, in 2013, have reported a case with aggressive NHL with chylous effusions in pleura and peritoneum [24]. Johnston et al reported that 15% of 584 patients had serous effusions determined by lymphomas, predominantly in male patients [25].

PE are more commonly in the various subtypes of T cell originated lymphomas while, only rare B cell lymphomas present pleural effusion [26, 27]. In patients with lymphoblastic lymphomas, 41.6% of have had pleural effusions compared with other subtypes where the percentage was only 3.8% [28]. PE in high grade malignant lymphomas are markers of poor evolution and prognosis [29-33].

As can be seen from the studies presented above, most patients with non-Hodgkin's malignant lymphoma and pleural effusion, as a major sign of onset or which occurs in the evolution of the disease have presented a significant personal history. Follicular lymphoma (FL) also called indolent lymphomas represent 20% of all NHL and the most frequent is a low-grade NHL [34].

The hallmarks of FL are: translocation t(14; 18)(q32; q21) in approximately 90% of cases; heterogeneous cytologic composition; most common and most frequent clinical features is lymphadenopathy; transformation into diffuse large B-cell lymphoma (DLBCL) and increase proliferation due to various genetic aberrations including *p53* mutations and inactivation of *p16.* Cellular expression in FL is characterized by the presence of CD10 (in 60% of cases) CD19, CD20, CD22, and surface immunoglobulin [35].

The patients with indolent lymphoma can be without symptoms or they can present fever, sweats or weight loss if the disease is expanded. Lymphadenopathy may have fluctuating evolution, appears and disappears; and there are seldom spontaneous remissions. Expansion of the disease into other organs is common and occurs especially in the skin, bones, marrow, gastrointestinal tract and central nervous system, but affecting the pleura and pericardium is atypical being encountered only in the aggressive forms [35].

Conclusions

The onset with pleural effusion is unusual for this type of indolent lymphoma in a patient without significant personal history and clinical features and probably announce the onset of transformation into DLBCL. This suspicion of the beginning of transformation is suggested by the presence of the pleural effusion from onset and a type B symptoms characteristic for aggressive lymphomas as well as of the relatively high value of LDH, a useful indicator of transformation.

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