Mediastinal Fibrosis and Hodgkin Lymphoma mimicking Bronchiolitis Obliterans Organizing Pneumonia

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Abstract

Bronchiolitis obliterans organizing pneumonia (BOOP) represents a kaleidoscope of concepts and morphologies, often being confused with a series of conditions, among which the most feared are Hodgkin's lymphoma and bronchioloalveolar carcinoma.
We shall present the case of a 56-year-old patient, diagnosed in August 2013 with a pulmonary tumour of the right upper lobe, which was CT staged - T4N0M0 (IIIA), who underwent a video-assisted thoracotomy for histopathological confirmation. A mediastino-pulmonary formation had been detected intraoperatively and multiple biopsies had been collected. The information brought by the histopathological examination suggested the presence of 2 synchronous pathologies, namely: the mediastinal biopsy showed an advanced degree of dense, compact fibrosis and the pulmonary biopsy highlighted the presence of granulation tissue and Masson bodies in the distal air space with destruction of vascular and alveolar structures, an aspect which was compatible with organizing pneumonia (BOOP). Once a diagnosis was established, an oral corticosteroid therapy was initiated (Prednisone 30 mg/ day) over a period of one month, but the symptomatology of the patient worsened. A new thoracic CT carried out in November 2013 highlighted the progression and extension of the paramediastinal tumoral formation, exhibiting central necrosis and invading the mediastinal vessels, causing their compression (superior vena cava syndrome) associated with multiple mediastinal and hilar adenopathies. The non-favorable evolution and the extensive array of conditions that may mimic the BOOP histopathological pattern have been the key elements, which were the basis of our persistence in getting a real diagnosis. Therefore, in this respect, the biopsy parts performed by thoracotomy were sent for immunohistochemical testing. The CD30 and CD15 positive markers distinctive for Reed-Sternberg cells allowed the diagnosis of Hodgkin's lymphoma.
Keywords: *Bronchiolitis obliterans organizing pneumonia (BOOP), Mediastinal fibrosis, Hodgkin's lymphoma.*

Rezumat

Bronșiolita obliterantă cu pneumonie in organizare (BOOP) reprezintă un caleidoscop de concepte și morfologii, fiind deseori confundată cu o serie de afecțiuni, între care cele mai de temut sunt limfomul Hodgkin și carcinomul bronhioloalveolar.
Prezentăm cazul unei paciente de 56 ani, diagnosticată în august 2013 cu tumoră pulmonară de lob superior drept stadializată CT - T4N0M0 (IIIA), la care s-a practicat toracotomie dreaptă video-asistata pentru confirmare histopatologică. Intra-operator s-a decelat o formațiune tumorală mediastino-pulmonară, prelevându-se biopsii multiple. Informațiile aduse de examenul histopatologic sugerau prezența a 2 patologii sincrone, și anume: biopsia mediastinală a arătat un grad avansat de fibroză densă, compactă, iar cea pulmonară a evidențiat țesut de granulație și corpi Masson în spațiul aerian distal cu distrucția structurilor vasculare și alveolare, aspect compatibil cu pneumonia de organizare (BOOP). O dată diagnosticul stabilit s-a inițiat terapie cu corticosteroid oral (Prednison 30mg/ zi) timp de o lună, însă simptomatologia pacientei se agravează. O nouă tomografie toracică efectuată în noiembrie 2013, pune în evidență progresia și extensia formațiunii tumorale paramediastinale, ce prezintă necroză centrală, invadează vasele mediastinale determinând compresia acestora (sindrom de venă cavă superioară) asociind multiple adenopatii mediastinale și hilare. Evoluția nefavorabilă și paleta extinsă de afecțiuni ce pot mima patternul histopatologic de BOOP au fost elemente cheie ce au stat la baza insistenței noastre de a obține un diagnostic real. Astfel, în acest sens, piesele de biopsii efectuate prin toracotomie au fost trimise pentru testare imunohistochimică. Markerii CD30 și CD15 pozitivi specifici pentru celulele Reed-Sternberg permit diagnosticul de limfom Hodgkin.
Cuvinte-cheie: *Bronșiolita obliterantă cu pneumonie în organizare (BOOP), fibroză mediastinală, limfom Hodgkin.*

Introduction:

Bronchiolitis obliterans organizing pneumonia (BOOP), also called "cryptogenic organising pneumonia", is an interstitial pulmonary condition that has rapidly become, despite its relative rarity, a common entity characterized by a non-distinctive histopathological pattern. The BOOP pathogenesis is more likely that of an inflammatory pulmonary disease, which combines plugs of granulation tissue placed inside the lamina of bronchioles and alveolar ducts, than a process of fibrosis such as in Usual Interstitial Pneumonia / Idiopathic Pulmonary Fibrosis (UIP / IPF)[1,2].

BOOP affects both sexes equally and may appear at any age. The clinical-radiological and histopathologically non-distinctive aspects may be associated with a variety of other conditions (table 1), which often leads to the delay of the diagnosis by 6-13 weeks[3,4].

The bronchoalveolar lavage (BAL) is indicated in all cases of suspected BOOP, being useful in the exclusion of other diagnoses. A joint model of cellular cytology, which is composed of a predominance of lymphocytes (20-40%), neutrophils (10%) and eosinophils (5%), may guide the diagnosis[5,6].

Table 1 Conditions mimicking BOOP

Postinfection	Chlamydia, Legionella, Mycoplasma, Adenovirus, Cytomegalovirus, Malaria, Pneumocystis, Cryptococcus, HIV
Drugs and substance abuse	Antibiotics, Amiodarone, b-Blockers, Cocaine abuse, Gold, L-tryptophan, Carbamazepine, etc.
Systemic inflammatory diseases	Rheumatoid arthritis, Polymyositis/dermatomyositis, Lupus erythematosus, Scleroderma, Behcet's syndrome, etc.
Other	Haematologic and immunologic malignancies
Organ transplantation	Bone marrow, lung, renal
Radiotherapy	
Miscellaneous	Lymphoma, cancer, myelodysplastic syndrome, primary biliary cirrrhosis, coronary artery bypass graft surgery

The pulmonary biopsy remains the gold diagnosis standard. There is no consensus regarding the optimal doses of treatment or its duration, but according to literature date, patients are treated with corticosteroids for at least 6-12 months[6,7]. The evolution towards pulmonary fibrosis may appear in 20% of patients and death in 5% of the cases[7,8].

The mediastinal fibrosis or fibrosing mediastinitis (FM) is a rare non-malignant condition characterised by slow progressive fibrosis and exuberant collagen formation in the mediastinum[9,10]. It may be idiopathic or secondary to some diseases, in particular infection with Histoplasma capsulatum[11]. Clinically and radiologically it imitates the malignant processes and may lead to the capture and compression of different structures in the mediastinum. Usually, it tends to be slowly progressive, with a variable prognosis depending on the degree of involvement of airways or large vessels. The surgical procedure is associated with a high risk of complications due to the dense strengthening of mediastinal structures and vascularisation.

There have been reports in specialized literature of attempts of placing stents in the occluded bronchi[11].

Clinical case

We shall present the case of a 56-year-old non-smoker female patient, with no personal medical history, who referred with a cough with muco-purulent expectoration for approximately 3 months as well as chest pain and exertional dyspnea, being admitted to hospital in August 2013. The patient did not have any history of fever, haemoptysis or other accompanying symptoms.

The clinical examination was within normal limits.

Biologically, the patient presented with leucocytosis (17,000/µl) and non-specific inflammatory syndrome. The microbiological tests for both the usual flora as well as tuberculosis were negative.

Radiologically, upon admission to hospital we noticed a right paratracheal opacity which caused the enlargement of the upper mediastinum and enlarged hili as well as ascension of the right hemidiaphragm (figure 1).

Respiratory functional assessment: normal respiratory volumes and flow rates (table 2).

Electrocardiogram: sinus rhythm with AV=78 bpm, with no terminal phase modifications.

Echocardiography: diastolic dysfunction of the left ventricle of the delayed relaxation type, ejection fraction of the left ventricle (FEVS)=50% without valvulopathies, left ventricular hypertrophy or pulmonary hypertension.

Abdominal and pelvic ultrasound: without space replacement processes at abdominal level, left ovarian cyst and uterine fibroid which require remote monitoring.

Arterial blood gas analysis: pH=7.37, Pco2=37 mmHg, Po2=81 mmHg.

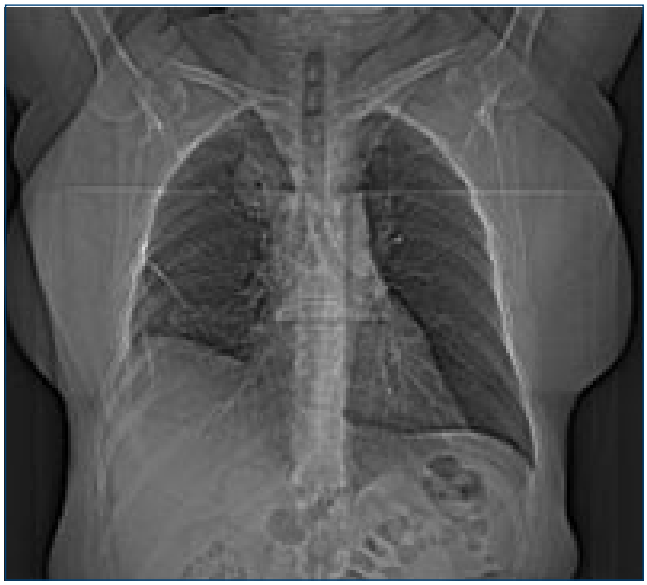

Figure 1: *Pulmonary radiography in posteroanterior incidence*

Bronchoscopy: congestion and mucosal oedema at the level of the bilateral segmental and sub-segmental bronchi, with no proliferative patent modifications in the explorable areas. Samples have been taken from the bronchial aspirate for usual flora, fungi and Mycobacterium tuberculosis with negative results, as well as those for neoplastic cells or cellular atypia.

In addition to the paraclinical evaluation a **new thoracic CT scan** was performed with a contrast medium

Table 2 Spirometry

Parameters	Predictive values	Predicted values (Pre)	% pred.	Post	% pred.	% diff.
FVC	2.52	2.99	119%	3.03	120%	1%
FEV1	2.12	2.94	139%	2.89	136%	-2%
FEV1/FVC	0.78	0.96	126%	0.95	122%	-3%
MEF 50	2.96	4.33	146%	3.88	131%	-10%

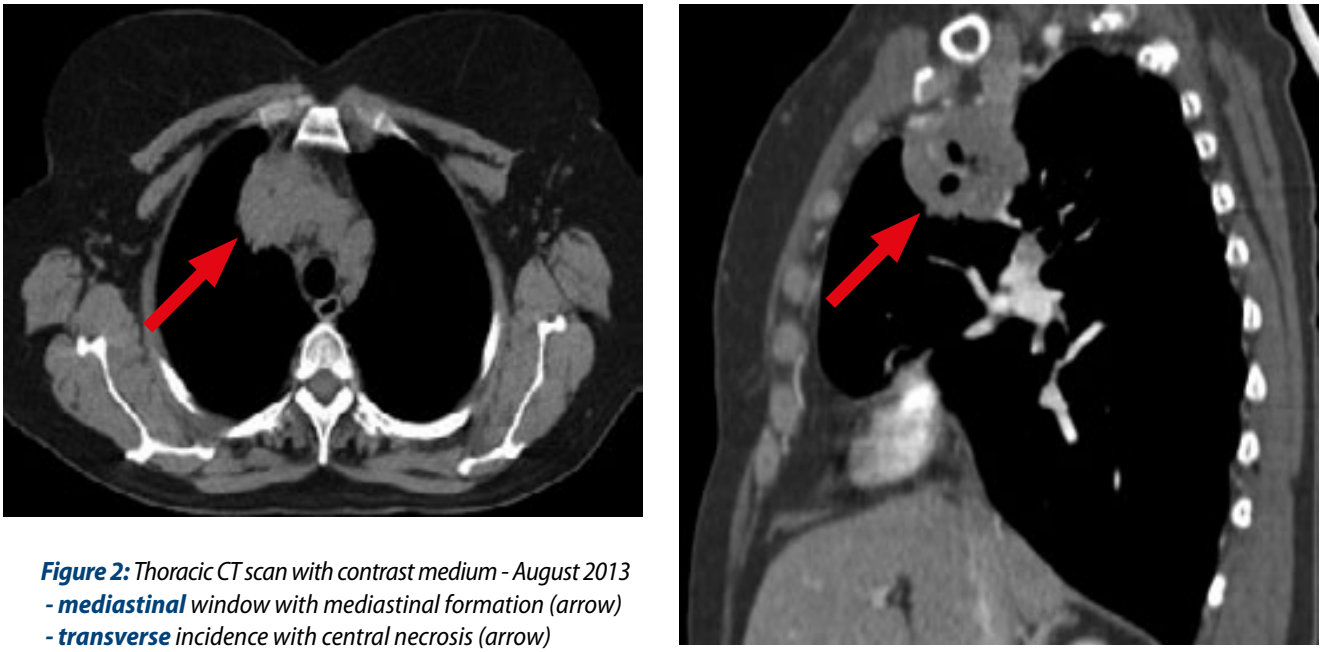

Figure 2: *Thoracic CT scan with contrast medium - August 2013*
*- **mediastinal** window with mediastinal formation (arrow)*
*- **transverse** incidence with central necrosis (arrow)*

that highlighted a tumor with a diameter of 37 mm located in the anterior segment of the right upper lobe (RUL), situated on the right lateral side of the upper mediastinum. This invades the intravascular mediastinal fat and, following the administration of the contrast medium, it shows large necrosis without mediastinal adenopathies. (figure 2).

The diagnosis has been RUL pulmonary tumour, CT staging: T4N0M0 (IIIA), with indication for surgical intervention both for obtaining the histopathological confirmation (HP) as well as for curative purposes. Therefore, the surgical examination establishes the indication for exploratory thoracotomy. Intraoperatively, several interpleural adhesions arranged apically and in antero-inferior mediastinum. The pulmonary parenchyma shows a tumor with a diameter of 3 cm, located in the anterior segment of the RUL, which is in continuity with a hard mediastinal formation, polylobate. This is located in the anterior-superior mediastinum and which causes the invasion of the superior vena cava (SVC) in the initial position with insinuation to the ascending aorta. Only partial dissection of the mediastinal tumour has been accomplished, due to the adhesions collected with SVC. Multiple biopsies have been collected from the lung, mediastinum and locoregional lymph nodes.

The extemporaneous examination revealed a non-specific inflammatory process.

The postoperative evolution has been favourable, with re-expansion of the lung and without the emergence of local or remote complications.

As a differential diagnosis, the etiologies of the two tumors have been taken into consideration, regarded as 2 synchronous tumours, namely:

for pulmonary tumor:

- infectious (pneumonia, abscess, tuberculosis)
- non-infectious (lung neoplasm, lymphoma, Wegener granulomatosis with polyangiitis, sarcoidosis)

for mediastinal tumor:

- retrosternal goitre, parathyroid adenoma, thymoma, lymphoma, haemangioma, tumours of germinal cells (dermoid cyst, teratoma)

The histopathological examination provides the following information:

Table 3 Cytology in the BAL liquid upon endobronchial re-evaluation

Cytology total no of cells = $6.6x10^6$	Results (%)	Normal values (%)
Macrophages	12.6	> 84
Lymphocytes	2.8	< 13
Granulocytes	84.4	< 3
Neutrophils	82.6	< 3
Eosinophils	1.8	< 0.5
Mastocytes	0.2	< 0.5

- ***the pulmonary fragment of the RUL:*** fibrous bands with moderate mixed inflammatory infiltrate, Masson type fibroblast buds in a few alveolar spaces as well as micro-abscesses. The described pattern of "organising pneumonia" with exudate of fibrin and neutrophils transforming into fibromyxoid masses with histiocytes and necrotizing changes in bronchi advocates for BOOP.
- ***the mediastinal fragment:*** fibrous conjunctive tissue rich in collagen fibres, important lymphocytic inflammatory infiltrate with deposits of fibrin at the surface, advocating for chronic fibrosing mediastinitis with calcification and abscessing areas (thymic rest on a part)
- ***ganglionic biopsy*** → reactive lymph nodes

According to the above mentioned investigations, it is worth mentioning that the pseudo-tumoral aspect is not pathognomic for BOOP and as specified before, there is a wide array of conditions that may mimic the same histopathological pattern with that of our case. In the absence of other elements suggesting an alternative diagnosis of the RUL tumour, the COP diagnosis is established accompanied by oral corticotherapy for a period of one month; however, the symptomatology of the patient aggravates. The unfavorable evolution shall impose reflection over the positive diagnosis. Investigations shall be resumed approximately 3 months after the establishment of the diagnosis, when the patient returns to our clinic. Endobronchially, we may speak of a stationary aspect, with absence of cellular atypia in the bronchoalveolar lavage (BAL) liquid, suggesting rather a suppurative process (table 2)

However, we do not encounter the same thing imagistically, where we may notice the progression and extension of the mediastinal tumoral formation with invasion of the vascular structures (superior vena cava, right venous brachiocephalic trunk, right subclavian artery) causing extensions in the thymic box and associating right mediastinal and hilar adenopathies. (figure 3).

The next step in elucidating the diagnosis was to conduct the immunohistochemical tests of the biopsy samples, which were initially collected through thoracoscopy. Although the histopathological aspect had been indicative of BOOP, in some cases it is not sufficient for the confirmation of the disease and must be supported by the respective immunohistochemical markers. In the present case, the identification of CD30 and CD15 positive markers distinctive for Reed-Sternberg cells allowed the conclusive diagnosis of Hodgkin's lymphoma.

The evolution of the patient in question had been unfavourable, the patient died before undergoing specific therapy for the lymphoma. The cause of death had not been the disease in itself but an overlapping of a fatal acute coronary syndrome.

Discussions

Cryptogenic organizing pneumonia(COP) (previously referred to as bronchiolitis obliterans organizing pneumonia or idiopathic bronchiolitis obliterans organizing pneumonia) is an idiopathic condition with frequently presents as an interstitial lung disease[12]. In the case presented, the BOOP diagnosis was also based on the exclusion of the conditions which might mimic this histopathological pattern. However, this had not been fully eloquent, which led to a delay in the final diagnosis. The arguments which advocated for the insistence in obtaining confirmation of the disease by means of immunohistochemical tests were: unfavourable clinical evolution and imaging with paradoxically no response to corticotherapy in the first month of treatment.

The aspect of "organising pneumonia" noticed on the biopsy samples represents in fact a process of non-specific tissue repair as a response to local or remote injury, under which different malignancies may hide. In fact, the case described manifests this particularity and remains a challenge for pulmonary specialists. The histopathological examination, which most of the times is essential in establishing the diagnosis and treatment guidance, has been a misguiding element because it only revealed COP lesions, masking the Hodgkin lymphoma typical changes. Probably one of the error factors has been the biopsy sample in itself, if its sampling has been performed from the periphery of the tumoral formation. The immunohistochemical tests bring additional information in such cases, but are not always accessible due to the high costs.

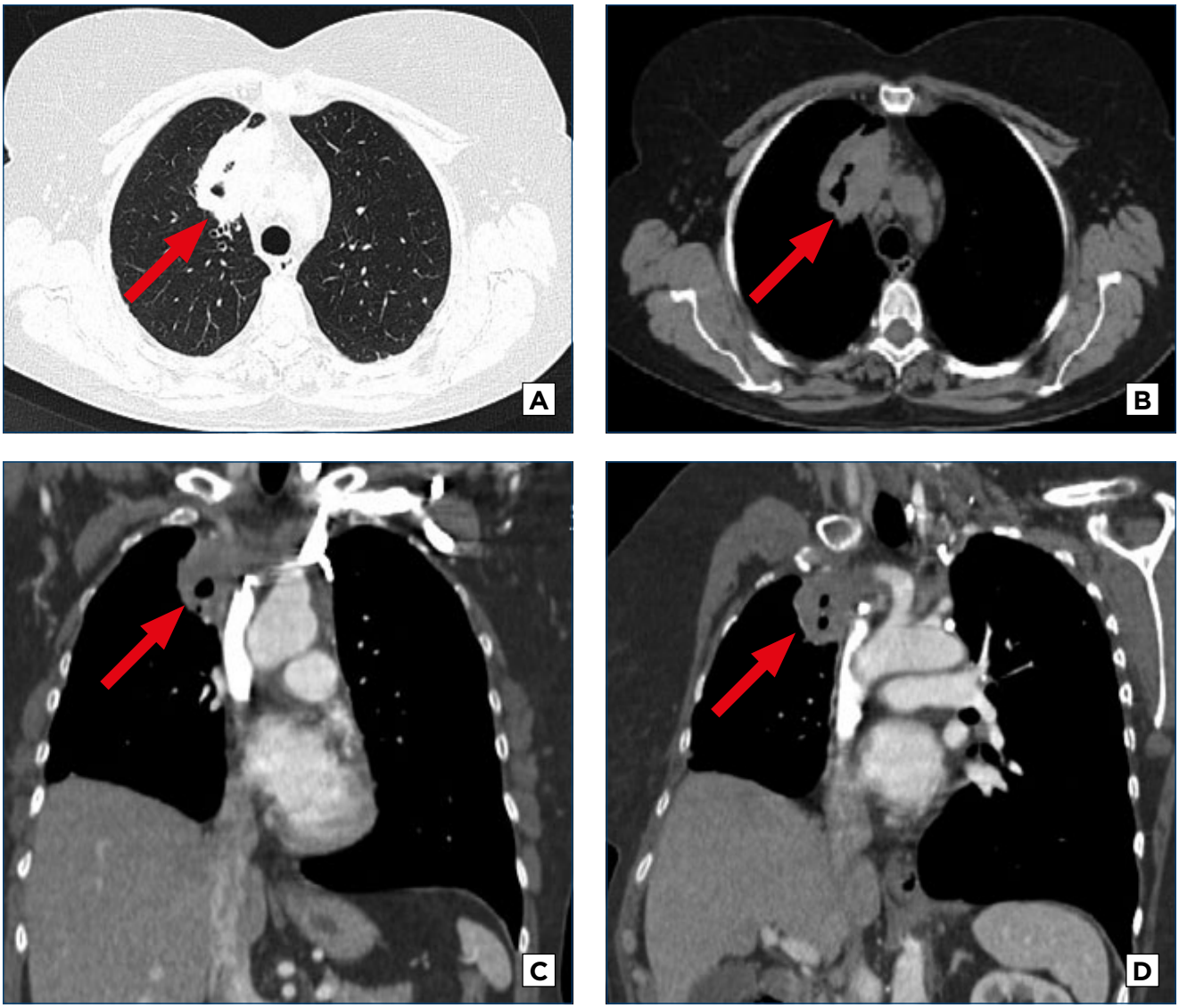

Figure 3: *Thoracic CT scan with contrast medium - November 2013*
Horizontal incidence: pulmonary (A) and mediastinal (B) window with tumoral formation with central necrosis and mediastinal adenopathies (arrow)
Transverse incidence: mediastinal window with SVC invasion (C) of the right venous brachiocephalic trunk and of the right subclavian artery (D).

Hodgkin's lymphoma (HL) is a lymphoid tumour representing less than 1% of all de novo neoplasms. Its incidence in the European Union is 2.3 and the mortality is 0.4 cases/100 000/year[13]. It affects slightly more men than women aged 20-40 years old; however, a second incidence peak is seen in individuals aged 55 and older. In terms of clinical, morphological, phenotypic and genotypic features, it is subdivided in classical HL (cHL) accounting for ~95% of all HL cases and nodular lymphocyte-predominant HL (NLPHL) representing ~5% of them[14,15].

Classical HL is characterized by four subtypes of the malignant process (nodular sclerosis, mixed cellularity, lymphocyte depletion and lymphocyte rich)[13,16]. It usually presents in the laterocervical lymph nodes, with peripheral extranodal involvement being very rare. A mediastinal mass is seen in most patients with nodular sclerosis cHL, at times showing the characteristics of "bulky" disease.

About 50% of patients are in stage I or II (table 3), but systemic symptoms (fever, night sweats, and body weight loss) are detected in approximately 25% of cases[13].

In contrast to earlier reports, the histological subtype is not regarded as a major prognostic indicator. Without treatment, cHL has a moderately aggressive clinical course[13]. With modern treatment strategies, 80%–90% of HL patients achieve permanent remission and can be considered cured[14,17].

For most patients with refractory or relapsed HL, the treatment of choice consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). The use of the antibody- drug conjugate brentuximab vedotin represents an option in patients failing ASCT. In some patients with localised late relapse, salvage radiotherapy alone appears to be sufficient[14,16,17].

Table 4 Definition of Hodgkin's lymphoma risk groups according to the European Organisation for Research and Treatment of Cancer / Lymphoma Study Association and the German Hodgkin Study Group[13]

Treatment group	EORTC/LYSA	GHSG
Limited stages	CS I–II without risk factors (supra-diaphragmatic)	CS I–II without risk factors
Intermediate stages	CS I–II with ≥1 risk factors (supra-diaphragmatic)	CS I, CS IIA with ≥1 risk factors; CS IIB with risk factors C/D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factors A/B, CS III/IV
Risk factors	(A) Large mediastinal mass (B) Age ≥50 years (C) Elevated ESR (D) ≥4 nodal areas	(A) Large mediastinal mass (B) Extranodal disease (C) Elevated ESR (D) ≥3 nodal areas

Elevated ESR: >50 mm/h without B symptoms, >30 mm/h with B symptoms.
Large mediastinal mass: more than one-third of the maximum horizontal chest diameter.
B symptoms: fever, night sweat, unexplained weight loss >10% over 6 months.
EORTC: European Organisation for Research and Treatment of Cancer;
LYSA: Lymphoma Study Association; **GHSG:** German Hodgkin Study Group;
CS: clinical stage; **ESR:** erythrocyte sedimentation rate.

Conclusions

Apparently a clear diagnosis of benign conditions can hide a disease with severe prognosis. Unfavourable evolution advocates insistence to obtain real diagnosis. The possibility of underlying neoplasia should be considered if initial presentation is not typical of BOOP (interstitial lung disease) and abnormal radiologic images persist in a patient with correctly treated BOOP as this association, although rare, may occur and should not remain undiagnosed. Unfortunately, initially mediastinal and pulmonary lesions didn't reveal the presence of Hodgkin's disease, which was later diagnosed by immunohistochemical tests CD15 and CD30 positive. In HL, personalised treatment based on certain genetic features as known for some malignancies is not established. Treatment intensity is chosen according to the clinical stage and the presence or absence of clinical risk factors. The use of risk adapted therapy has led to excellent cure rates in HL patients irrespective of the stage at diagnosis. Unfortunately, in our patient the initial pathologic confusion with BOOP led to a delay in diagnosis that proved to be fatal. ■

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