Transesophageal ultrasound (EUS)–guided fine needle aspiration (FNA) in the diagnosis of Lymphomatoid Granulomatosis

Agoaspirato (FNA) in corso di ecoendoscopia (EUS) nella diagnosi della granulomatosi linfomatoide

Valentina Conti[1] *(foto)*
Carlo Gurioli[1]
Andrea Rossi[2]
Gianluca Casoni[1]
Sara Piciucchi[3]
Alessandra Dubini[4]
Marco Chilosi[5]
Venerino Poletti[1]

[1] Department of Diseases of the Thorax, Ospedale G.B. Morgagni-L. Pierantoni Hospital, Forlì; [2] Department of Medical Sciences, Pulmonology Unit, University of Verona, Verona; [3] Radiology, G.B. Morgagni-L. Pierantoni Hospital, Forlì; [4] Pathology Unit, G.B. Morgagni-L. Pierantoni Hospital, Forlì; [5] Department of Anatomic Patology, University of Verona

Summary

72-year-old Caucasian man, with negative history of respiratory diseases, was admitted to our Department for dyspnoea, night sweats, fever and acute respiratory failure. Laboratory findings (including blood cultures and autoimmunity) showed mild increase of C reactive protein (CRP) and mild lymphopenia. The imaging with chest X ray, confirmed by chest CT scan revealed bilateral consolidations. Bronchoalveolar lavage (BAL) was negative for bacteria and fungi and showed lymphocytosis, transbronchial lung biopsies revealed pattern suggestive for organizing pneumonia (OP). The patient was treated with systemic corticosteroids, with clinical and radiologic improvement, and discharged with a diagnosis of possible cryptogenic OP. After two months, patient was readmitted to hospital because of acute respiratory failure and fever. Positron Emission Tomography/Computed Tomography (PET/CT) scan showed high uptakes in area of alveolar opacity in the right lung lower lobe (SUVmax = 3.78), and in nodular lesion of the left adrenal gland (SUVmax = 6.85). Transesophageal ultrasound (EUS) was performed, with a EUS-guided fine needle aspiration (FNA) of the left adrenal gland, revealing at cytology and cell block results the diagnosis of Lymphomatoid Granulomatosis (LYG).
In this case, EUS-FNA allowed the final diagnosis of LYG by the sampling of an extra-thoracic lesion, underlying the importance of the use of this procedure in identifying lymphoproliferative diseases.

Riassunto

Uomo caucasico, 72 anni, con anamnesi negativa per disturbi respiratori è stato ricoverato nel nostro dipartimento per dispnea da sforzo, sudorazione notturna, febbre ed insufficienza respiratoria acuta. Gli esami ematochimici (inclusi emocoltura e autoimmunità) mostravano solo moderato incremento della proteina C reattiva (PCR), e moderata linfopenia. La radiografia del torace, confermata dalla tomografia computerizzata (TC) rivelava diffuse aree di consolidazione polmonare bilaterali. Il lavaggio broncoalveolare, negativo per batteri e miceti, mostrava linfocitosi, inoltre la biopsia transbronchiale rilevava un pattern suggestivo di polmonite organizzata (OP). Il paziente è stato trattato con steroidi sistemici, con rapido miglioramento clinico e radiologico, e successivamente dimesso con diagnosi di possibile criptogenetica OP. Dopo due mesi dalla dimissione, il paziente è stato nuovamente ricoverato per insufficienza respiratoria acuta e febbre. Tomografia ad emissione di positroni/TC (PET/TC) evidenziava un'area di iperfissazione del tracciante a livello di un'opacità alveolare nel lobo polmonare inferiore di destra (SUM max = 3,78) e in una lesione nodulare a livello della ghiandola surrenalica di sinistra (SUV max = 6,85). È quindi stato eseguito esame ecoendoscopico (EUS) con agoaspirato mirato (FNA) della lesione surrenalica con riscontro su esame citologico e citoincluso di granulomatosi linfoide (LYG).
In questo caso, il campionamento di una lesione extratoracica mediante EUS-FNA ha permesso diagnosi di LYG, sottolineando l'importanza dell'uso di tale procedura nell'identificazione dei disordini linfoproliferativi.

Key words
Interstitial lung disease • Lymphoproliferative disorder • Bronchoalveolar lavage • Surgical lung biopsy

Parole chiave
Malattia interstiziale polmonare • Disordine linfoproliferativo • Biopsia polmonare chirurgica

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Venerino Poletti
Department of Diseases of the Thorax
Ospedale G.B. Morgagni-L. Pierantoni Hospital
Via Carlo Forlanini 34
47121 Forlì (FC)
venerino.poletti@gmail.com

Introduction

LYG is a rare condition that affects mainly the lungs, but also numerous other sites i.e. central nervous system, skin, liver, kidney appearing in an adult male population [1]. It is considered an Epstein-Barr virus (EBV) driven T cell rich-B cell lymphoproliferative disease that affects mainly the lungs [2].

LYG is an Epstein-Barr virus (EBV) driven T cell rich-B cell lymphoproliferative disease that affects mainly the lungs.

The clinical presentation includes systemic manifestations such as fever, weight loss, skin lesions, mimicking infectious diseases (e.g. tuberculosis), va-

sculitis, metastatic malignancies or autoimmune disorders [1].

EUS and EUS-FNA is a procedure used by gastroenterologists and cardiologists, which has been increasingly adopted in the last decade by pulmonologists, especially for diagnosis and staging of nonsmall cell lung cancer (NSCLC), and also for non-neoplastic diseases e.g. granulomatosis diseases (sarcoidosis, tuberculosis, etc). EUS-FNA allows to visualize structures below the diaphragm as well as the left adrenal gland [3].

A case of pulmonary LYG with extra-thoracic involvement, which diagnosis was made by a left adrenal gland cyto/histology obtained through EUS-FNA is presented.

Case report

72-year-old man, mild former smoker (< 5 pack-years), ex school caretaker, was admitted to our ward, because of the onset of rapidly worsening exertional dyspnoea, night sweats, fever and acute respiratory failure. A chest X-ray (CXR) was performed, detecting a diffuse bilateral interstitial involvement, and consolidations of the lower left lobe.

His past medical history was characterized by systemic hypertension (chronically treated with bisoprolol 1.25 mg/*die*) and hypercholesterolemia (simvastatin 20 mg/*die*).

Symptoms declared were fever (37.8°C), and fatigue. The respiratory rate was 26 b/min, blood pressure 120/80 mmHg, heart rate 70 beats/min, oxygen saturation on pulse-oximeter 80% while breathing room air. Chest examination showed markedly reduced breath sounds, with bilateral basal inspiratory crackles, and lower limbs peripheral oedema was present.

Routine laboratory tests were within the normal range except for a decreased total white blood cells count of $3.30x10^9$/L (n.v. 4.00 – 10.00), mild lymphopenia $0.64x10^9$/L (n.v. 1.00 – 4.00), and increased CRP 28 mg/L (n.v. < 5.0). Blood cultures, urinary antigens for *Streptococcus pn*. and *Legionella pn*., and autoimmunity were negative. Arterial blood gases analysis performed while breathing room air demonstrated hypoxemia, with uncompensated respiratory alkalosis (pH 7.49, $PaCO_2$ 32.8 mmHg, PaO_2 41 mmHg, SpO_2 79%).

In the suspicion of pulmonary embolism (PE) a computed tomography angiography was performed, showing absence of PE. However lung window showed diffuse pulmonary infiltrates characterized by multiple partially confluent nodules, mostly of them showing a ground glass attenuation, ranging from few millimetres to about one centimetre in size. A mild interlobular septal thickening was also present particularly evident in the upper lobes and in the costophrenic angles. A diffuse ground glass attenuation was present particularly in the apicodorsal segment of left upper lobe, lingula and both lower lobes, mainly in the midollar region of the lungs. Some mediastinal and hilar enlarged lymph node (max axis of the right hilar lymph node = 20 mm, subcarinal 22 mm) (Figure 1a).

A bronchoscopy was performed, with bronchoalveolar lavage (BAL) and transbronchial lung biopsies (TBLB). BAL showed increased total cell count (cells/ml 150.000), mild lymphocytosis (total lymphocytes 20%, T lymphocytes CD3+ = 93%, CD3+CD4+ = 28%, CD3+CD8+ = 58%, macrophages 70%, neutrophils 10%). Cultures and immunofluorescence test for bacteria, mycobacteria, fungi and respiratory virus (Cytomegalovirus, Adenovirus, Herpes virus type I, Respiratory Syncytial Virus) were negative. TBLB performed at the left lower lobe showed peribronchial lung tissue with lymphoplasmacitic infiltrate, hystiocytes, and a focus of organizing pneumonia. No any atypical lymphoid infiltrate was observed (Figure 1b).

A diagnosis of cryptogenic organizing pneumonia

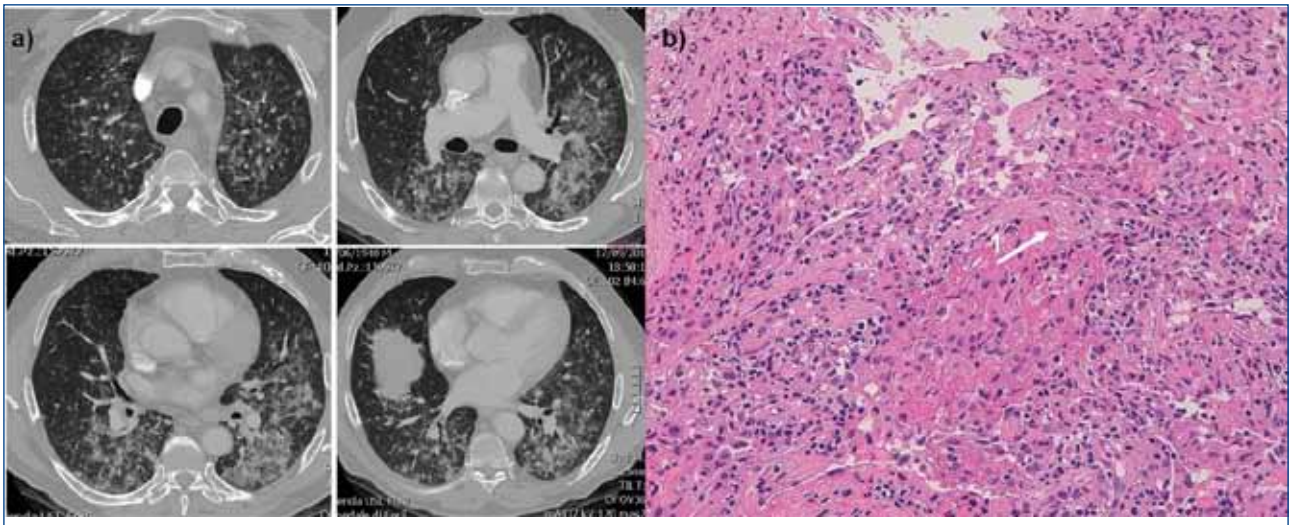

Figure 1. a) Bilateral thickening of the intra and interlobular interstitium, mainly at the lower lobes, with a ground glass pattern, and presence of widespread and micronodules. b) Peribronchial lung tissue with lymphoplasmacitic infiltrate, foamy hystiocytes, and 1 focus of OP (arrow 1).
Immunohistochemistry for lymphoma was negative (AE1-AE3, CD20, CD5, CD30).

(COP) was made and the patient was treated during hospitalization with high dose systemic corticosteroids i.v. (methyl-prednisolone 60 mg/*die*) with evident clinical and radiologic improvement. He was discharged after 13 days with normal gas exchange (SpO_2 = 97% while breathing room air), with treatment with oral prednisone (50 mg/*die* tapering dose for a total of 20 days).

Two months after discharge, the patient was still under treatment with oral prednisone (12.5 mg/*die*) and he noted the appearance of dyspnoea and fever. He consequently presented to hospital with recurrence of acute respiratory failure. Chest examination was negative, and oedema of lower extremities was present. SpO_2 was 84% while breathing in room air. A new CXR showed parenchymal consolidations of the left lung, absence of pleural effusions. Echocardiogram was negative, with value of pulmonary systemic artery pressure estimated at 24 mmHg. Routine laboratory tests showed N-terminal pro-B-type natriuretic peptide (NTpro-BNP) 841 ng/L (n.v. < 900), a decrease of total white blood cells (1.59x10^9/L), with neutropenia and lymphopenia, and anemia (Hb = 9.4 g/dl), a decrease of platelets (67x10^9/L), increased values of CRP (28.4 mg/L), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), ferritin (3000 mcg/L, n.v. 30-400) and β2-microglobulin (6.4 mg/L, n.v. 0.8-2.2). Hepatitis B and C, and HIV serologies were negative. Serologic Epstein Barr virus VCA and EBNA IgG were positive (750 U/ml and 600 U/ml, respectively).

Bone marrow biopsy was performed in the suspicion of a lymphoproliferative disease, showing hematopoietic tissue with slight reduction in myelopoiesis, nodular non-necrotizing epithelioid granulomas. Abdominal ultrasound was normal, except for a spleen size upper the normal limit, with longitudinal diameter 13 cm.

The PET/CT scan showed a high pulmonary uptake in a nodule of the right lower lobe, and in the left adrenal gland.

The patient underwent directly to PET/CT because the CXR showed already changes than previous similar exam. The PET/CT scan which showed a high pulmonary uptake in a nodule of the right lower lobe, and in the left adrenal gland (Figure 2a). A CT-guided lung biopsy was performed, showing pulmonary alveolar parenchyma with focal lymphoid infiltrate and aspects of vascular infiltration. The finding was too small for a definitive diagnostic evaluation.

Finally, based on the left adrenal gland PET/CT scan finding, a EUS was performed showing a hypoechogenic area of 15x10 mm compatible with a nodule in the left adrenal gland. EUS-FNA (4 samples of FNA) results obtained by cytology and cell block examination showed normal adrenal gland tissue, together to necrotic areas, and a interstitial lymphoid infiltrate consisting of a small number of EBV-positive B cells admixed with prominent inflammatory background with T cells (CD3+) (Figure 2b). After the procedure laboratory test showed stable reduction of white blood cells count of 3.20 x 10^9 (n.v. 4.00-10.00) and platelets 169 x 10^9 (n.v. 140-400).

The final diagnosis was angiocentric and angiodestructive EBV-driven B-lymphoproliferative disease, diagnostic for LYG. Eventually the diagnosis was continued in a surgical lung biopsy sample.

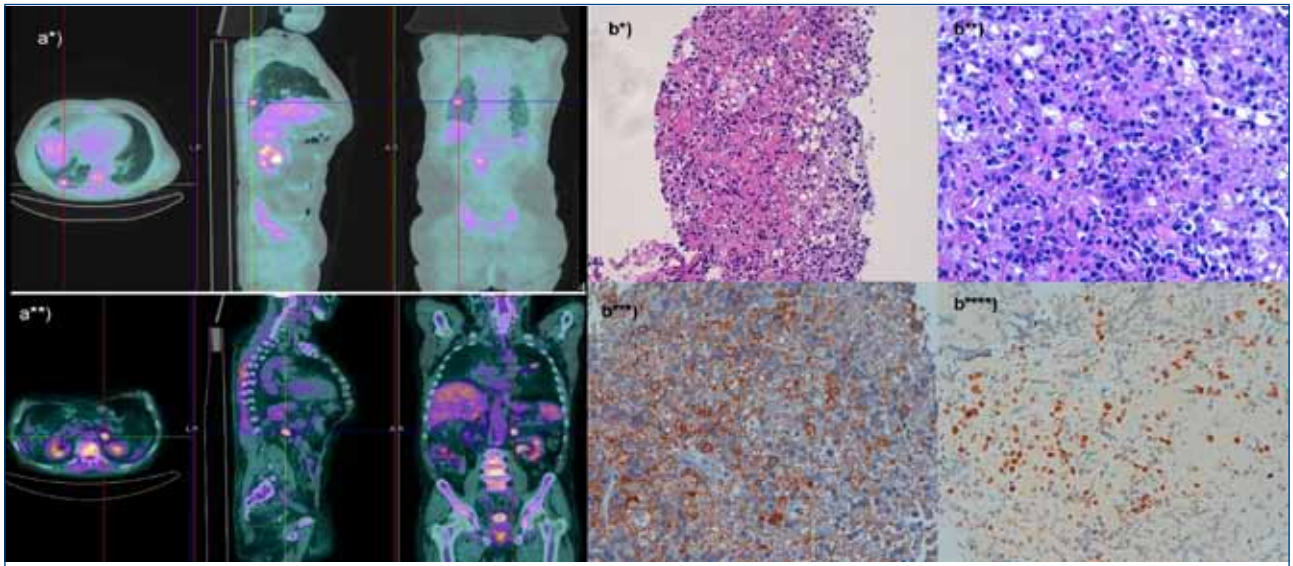

Figure 2. a) PET/CT SCAN: high pulmonary uptake in a nodule of the right lower lobe (*), and in the left adrenal gland (**) b) *Cell block: adrenal cortical tissue with an atypical lymphoid infiltrate (H&E, low power). ** The atypical lymphoid cells are better seen at higher power (H&E). *** Large cells express the CD20 marker typical of B cells. **** These cells are EBER + (encoded RNA positive).

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The patient was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone but he died after 4 months from the diagnosis.

Discussion

LYG includes a group of related lesions characterised by infiltration of the affected tissue by a heterogeneous cell population composed of a large number of reactive T-cells, a variable proportion of large EBV-infected B-cells (as defined by the expression of B-cell related antigens CD20 and CD79a), EBV markers, such as latent membrane protein-1 and EBV-encoded RNA1,2,4. LYG needs to be distinguished histologically from other diseases characterised by polymorphous lymphoid infiltration (e.g. IgG4-related sclerosing disorders, angio-immunoblastic lymphoadenopathy, acute and fibrinous organising pneumonia, inflammatory sarcomatoid carcinoma, and other malignant lymphomas, in particular enteropathy-associated T-cell lymphoma and acute T-cell lymphoblastic leukaemia), and/or by local coagulative necrosis and prominent angioinvasion (including extra nodal T-/NK- (nasal type) lymphoma, polyangioitis and granulomatosis) [4].

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LYG more frequently affects males and typically presents in the fifth decade. However, occurrence in childhood has been documented, as well as in the immunosuppressed subjects [5]. Affected patients most frequently show evidence of lung involvement, followed by central nervous system, skin, liver, and kidney.

As for systemic presentation of lymphoma B-related symptoms, patients with LYG present with fever (60%), weight loss (35%), and malaise (35%). Rarely, patients may be asymptomatic. Generally, chest physical examination is normal, and laboratory data are not specific [1].

Data indicate that lymphomatoid granulomatosis is now considered an EBV driven lymphoproliferative disorder of B cell [6].

In the presented case, an autoimmune disease has been excluded with laboratory test that detect negative profile for anti-DNA antibodies, anti-nuclear (ANA) antibodies, anti-extractable nuclear antigens (ENA) antibodies, Anti-Neutrophil Cytoplasmic (ANCA) antibodies, rheumatoid factor.

The suspicion for a lymphoproliferative disorder was based on the recurrence of symptoms and a relapse of respiratory failure, maybe due to the reduction of systemic corticosteroid doses, and the procedure which gave evidence for the diagnosis was EUS-FNA of the left adrenal gland. The presence on bone marrow biopsy of nodular non-necrotizing epithelioid granulomas was not specific in the lymphoproliferative disorder; this findings has already been reported and usually is clinical not relevant [7].

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EUS has extended the opportunity to study thoracic diseases when abnormalities belong to anatomical sites located close to the esophagus, or under the diaphragm. The ability to sample liver, spleen, left adrenal gland, para-aortic and perigastric lymph nodes is well documented in the literature [8]. The ability to perform fine needle aspiration/biopsy of adrenal lesions with EUS acquisition is even more recent [9].

In the presented case, the feasibility of EUS guided–FNA for extra-pulmonary lesions was highlighted. Adequate tissue samples using EUS guided-FNA with a standard 22G FNA needle was obtained via transesophageal approach, and the close proximity and direct visualization of the left adrenal gland allowed a simpler and quicker procedure, as compared to the percutaneous method, without complications. The benefit of endobronchial ultrasound (EBUS) and EUS in the diagnosis of lymphoma's has been highlighted in a number of case studies. The utility of EUS-FNA has been already demonstrated also for patients with renal mass. However, the lack of tissue architecture obtained by cytological FNA specimens might decrease the diagnostic accuracy in the diagnosis of lymphomas, although relatively simple adjustment to routine FNA sampling may help the diagnostic yield [10].

In this case, EUS-FNA demonstrated the characteristic triad for LYG: polymorphic lymphocytic infiltrate, angiitis due to transmural infiltration of arteries and veins by lymphocytes, and granulomatosis [11]. Moreover, immunohistochemistry confirmed the diagnosis. In the sample obtained the density of EBER+ and CD20+ cell was high and was assessed in cell blocks that may be considered a histological preps [12].

In conclusion, in this case of a rare left adrenal involvement of LYG, EUS-FNA allowed the final diagnosis of the disease by the sampling of an extra-thoracic lesion, underlying the importance of the use of this procedure for pulmonologists.

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Gli Autori dichiarano di non avere alcun conflitto di interesse con l'argomento trattato nell'articolo.