

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports





Endobronchial ultrasound-guided transbronchial needle aspirate for diagnosis of anaplastic large cell lymphoma of unusual presentation: A case report



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ARTICLE INFO

NonHodgkin lymphoma

Anaplastic large cell lymphoma (ALCL)

Anaplastic lymphoma kinase (ALK)

Rapid on-side evaluation (ROSE)

Keywords:

EBUS-TBNA

A B S T R A C T

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL) originated from mature post thymic T cells. They represent 1–3% of NHL. Different subtypes have been described: Anaplastic lymphoma kinase (ALK)-negative ALCL, ALK-positive ALCL and breast implant-associated ALCL. ALK-positive ALCL affects mainly the young and has better prognosis. We present a case report of an adult woman with AKL-positive ALCL, diagnosed by endobronchial ultrasound-guided transbronchial needle aspirate (EBUS-TBNA).

A 59-year-old women with no history of breast implants, was admitted for a four-month low back pain. Initially, the patient was treated for a spondyloarthropathy, but due to persistence of the symptoms, a lumbosacral MRI was performed, showing changes in morphology and signal intensity in the vertebral body of L3, along with edema and a paravertebral collection that affected the left psoas muscle, suggesting granulomatous spondylodiscitis. Chest CT-scan showed mild left pleural effusion, subcarinal and right hiliar adenomegalies. An EBUS-TBNA with ROSE (rapid on-site evaluation) was performed showing positive findings for malignancy, suggestive of hematolymphoid neoplasia. Pathology analysis showed an AKL-positive ALCL. Additionally, a biopsy of paravertebral tissue biopsy was obtained, which was consistent with the nodal sample. Chemotherapy was initiated with the CHOP protocol: cyclophosphamide, hydroxydaunorubicin, vincristine sulfate and prednisone.

EBUS-TBNA is a minimally invasive and safe technique for obtaining mediastinal samples. Collaboration with a cytopathologist trained to perform ROSE improves the diagnostic performance.

1. Introduction

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL) originated from mature post thymic T cells. They represent 1–3% of NHL. Different subtypes have been described: Anaplastic lymphoma kinase (ALK)-negative ALCL, ALK-positive ALCL and breast implant-associated ALCL [1].

ALK rearrangements with NPM1 and other partners are the most common and best characterized rearrangements among hematologic malignancies [2]. Most of the ALK-positive ALCLs have a t(2; 5) (p23;

q35) fusing the ALK gene to NPM1; but these translocations can also occur with other partner genes, resulting in ALK fusion with TPM3, TPM4, TFG, ATIC, among others [3,4]. These fusion partners determine the intracellular localization of the fusion protein. The NPM-ALK fusion protein activates various signaling pathways in ALK-positive ALCL cells, including the JAK/STAT3, PI3K/AKT/mTOR, among other pathways [5], and has been shown to result in accumulation of oncogenic CDC25A and MCL1 via a phosphorylation-dependent reaction. Other mechanisms via transcription factors such as the CCAAT enhancer binding protein (C/EBPβ) have also been shown to affect survival and growth of

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https://doi.org/10.1016/j.rmcr.2020.101027

Received 3 December 2019; Received in revised form 13 February 2020; Accepted 20 February 2020 Available online 22 February 2020 2213-0071/© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-ad/4.0/).

Table 1

Laboratory results.

	Result	Reference range
Leukocyte count	20560/µl	4230-9070
Neutrophils	16580/µl	1780-5380
Lymphocytes	2780/µl	1320-3570
Monocytes	940/µl	30-820
Eosinophis	20/µl	40-540
Basophils	40/µl	10-80
Hemoglobin	13.1 gr/dL	13.7-17.5
Hematocrit	43.3%	40.1–51
Platelet count	594.000/µl	163.000-337.000
Serum creatinine	0.59 mg/dL	0.67-1.17
Ureic nitrogen	14.8 mg/dL	6–20
C-reactive protein	16.07 mg/dL	0-0.5
HIV antibodies	0.18 (Non reactive)	0-0.99
Direct BK in sputum N. 3	Negative	

ALK-positive ALCL neoplasms [6].

ALK-positive ALCL affects mainly the young, with a men:women ratio of 1.5:1. It is most frequently diagnosed in North America and has a better prognosis when compared to other subtypes. Extra nodal compromise is common (60% of cases), including lungs, soft tissue, bone and bone marrow [7].

EBUS-TBNA is a minimally invasive procedure designed to assess adenomegalies and mediastinal masses. It has been established as a reliable procedure for lung cancer diagnosis and stratification, with a sensitivity of 91% and a specificity of 100%. The yield for lymphoma diagnosis is lower, with a sensitivity of 66.2% and a specificity of 99.3% [8,9]. Nevertheless, the implementation of rapid on-site evaluation (ROSE) has become a complementary practice to EBUS-TBNA, which secures a proper sample, allowing an adequate diagnosis and reducing healthcare costs, avoiding more complex diagnostic procedures [9]. We present the case of a 59-year-old woman with ALK-positive ALCL diagnosed by EBUS-TBNA plus ROSE.

2. Case report

59-year-old woman, with arterial hypertension and smoking history, no other morbidities, nor breast implants. She consulted for a fourmonth low back pain and one-month night sweating, productive cough with yellowish sputum production, a left submandibular lymphadenopathy and fever. She was initially treated as a case of spondyloarthropathy. Due to persistence of low back pain, a lumbosacral MRI was performed, which showed changes in morphology and signal intensity of the vertebral body of L3, along with edema and a paravertebral collection which extended to the left psoas muscle suggesting spondylodiscitis of granulomatous origin.

On physical examination she had a blood pressure of 140/90 mmHg, heart rate of 90 bpm, respiratory frequency of 16 rpm, 39 °C temperature, a painless left submaxillary adenopathy without inflammation, occasional bi-basal expiratory wheezes in both lungs, lower back pain at mobilization. The rest of the physical exam was unremarkable. Laboratory blood tests showed increased acute-phase reactants (Table 1).

Chest radiograph showed a left mild free-flowing pleural effusion, partial passive atelectasis in the lower lobe, normal pulmonary parenchyma, and adenomegalies in multiple mediastinal stations, mainly in station 7 and in right pulmonary helium, where conglomerates were found (Fig. 1A, B, C,D). Due to these radiological findings along with fever, a chronic granulomatous disease was suspected. EBUS-TBNA plus ROSE is performed, allowing sampling of the subcarinal region (Fig. 2). Pathology report revealed a morphological pattern and immunohistochemical expression profile compatible with AKL-positive ALCL.

Immunohistochemistry (IHC) showed neoplastic cells with diffuse reactivity to CD30 and MUM1, with focal reactivity to CD4. There was no expression of CKAE1-AE3, LMP1, CD3, CD20, PAX5, CD15, CD45, CD8, CD56, CD38 and BOB1. Such expression matches with the paravertebral biopsy, which reported fibroconnective tissue diffusely infiltrated by a malignant neoplasm, of large and pleomorphic cells, of



Fig. 1. A. Subcarinal nodal conglomerate. B, C. Paratracheal and pre-tracheal nodal conglomerate. D. Left pleural effusion.



Fig. 2. EBUS-TBNA. Vocal cords are observed. The blue arrow shows an adenomegaly, the red arrow shows the needle within the adenomegaly, the yellow arrow shows a subcarinal nodal conglomerate in station 7. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

anaplastic characteristics, with irregular nuclei and some binucleated cells with prominent nucleoli, granular chromatin and broad eosinophilic cytoplasm with a tendency to cohesivity and diffuse growth pattern.

In this case, IHC reported malignant cells positive to CD30 (90%), MUM1 (70%), ALK (90% with cytoplasmatic staining), EMA, cyclin D1 and CD4, with loss of CD3 and CD2 markers. Cells were negative to CD38, CD138, Kappa, Lambda, CD56, CD8, CD15, CD10, CD117, CKAE1/AE3, CD20, PAX5, SOX11, SOX10, IgG, SALL4, PLAP, OCT3-4. Ki-67 proliferation index was 80%. In situ hybridization for Epstein Barr virus RNA (EBER-ISH) was negative (Fig. 3).

The patient was diagnosed with ALK-positive ALCL. She was assessed by hematology-oncology and chemotherapy was initiated with the CHOP protocol (cyclophosphamide, hydroxydaunorubicin, vincristine sulfate and prednisone). During treatment, she presented increase in the pleural effusion, which required drainage without further complications.

3. Discussion

Anaplastic large cell lymphoma is responsible for approximately 3% of T cell lymphomas worldwide. ALCL represents 3–5% of all NHL, with an annual incidence of 0.2–0.25/100,000 per year [1]. The most common histological pattern is a diffuse proliferation of large neoplastic

cells, which are markedly atypical and produce a diffuse alteration of normal ganglionic architecture. ALCL tumors are characterized by the expression of CD30. The expression of ALK in ALCL tumors can be nuclear, cytoplasmatic or both [10,11]. Five morphologic patterns have been described in ALK-positive ALCL: a common pattern of large cells (60% of cases), lymphohistiocytic (10%), small cells (5–10%), Hodking-like (3%) or a combination of more than one of the above (15%) [12].

Patients diagnosed with ALK-positive ALCL are typically young (around 20–30 y/o), with a male predominance. Extra ganglionic disease is frequent, which may include digestive tract, pulmonary parenchyma, axial skeleton, liver and skin. Unspecific symptoms and fever may be present in up to 75% of cases [13]. Prognosis of this subtype is superior to that of other T cell lymphomas. This case is uncommon, for it presented in a woman at an unusual age.

It has been recognized that 60% of patients with ALK-positive ALCL present with extra nodal disease [7]. CHOP protocol is still the most used initial therapy. Results from the international peripheral T cell lymphoma showed that the overall response rate (ORR) with CHOP is 70%–80% with a response rate of around 90% in ALK-positive ALCL, with a 5-year progression-free survival (PFS) exceeding 60% [14]. Brentux-imab vedotin (BV), a monoclonal antibody that binds to CD30 and causes tumor cell apoptosis, is also used in refractory or relapsed ALCL, and it has also been studied for allogenic transplant. Recent studies have



Fig. 3. ALCL AKL positive. A, B. Hematoxylin and eosin cell block coloring, sample from station 7 with evidence of malignant neoplasm of hematolymphoid origin composed by anaplastic lymphocytes. C. Immunohistochemistry technique: CD30 positive expression. D. immunohistochemistry technique: ALK-1 positive expression. E, F. Hematoxylin and eosin staining with a vertebra sample demonstrating malignant neoplasm of hematolymphoid origin, composed by anaplastic lymphocytes. G. Immunohistochemistry technique: CD30 positive expression. H. immunohistochemistry technique: ALK-1 positive expression.

shown that the median PFS in patients treated with BV was significantly longer than the PFS of the most recent prior therapy in T cell lymphoma with CD30 expression [14,15].

EBUS-TBNA is a minimally invasive bronchoscopic procedure used to achieve lymph nodes and mediastinal masses sampling [16]. It has been recognized as a reliable and cost-effective procedure for diagnosis and stratification of lung cancer, with a high sensitivity and specificity. Even though sensitivity is lower for the diagnosis of lymphoma, the American College of Chest Physicians recommend EBUS-TBNA in patients with enlarged hilar or mediastinal lymph nodes, when lymphoma is suspected [8,9,17].

In some hospitals, like ours, ROSE is used as a complementary technique to EBUS-TBNA, in which a pathologist performs an ultra-rapid Diff-Quick staining and direct real-time visualization [18]. With this method, quality of the sample can be determined, as well as its inflammatory, tumoral or immunoproliferative characteristics [19,20]. ROSE reduces procedure time and exposure to anesthetic agents, therefore reducing possible complications and healthcare costs. Despite the above, some studies report contradictory evidence regarding the benefits of EBUS-TBNA plus ROSE [9,21]. Nevertheless, in our experience, we have seen an improvement in diagnostic performance, using a minimally invasive and safe procedure with increasing application in the diagnosis of lymphoma.

Ethics approval and consent to participate

This report was prepared in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration. We have approval letter of Ethics Committee in biomedical research IRB/EC No. 307–2019 of the Fundación Valle del Lili to publish this manuscript.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The datasets used and/or analyzed during this case report are available from the corresponding author on reasonable request.

Funding

No funding sources were used.

Declaration of competing interest

The authors declare that they have no competing interests. This manuscript has not been published and is not under consideration for publication elsewhere. Additionally, all of the authors have approved the contents of this paper and have agreed to the journal's submission policies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101027.

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