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Elevated Adenosine Deaminase in Pleural Effusion
A Case of Non-Hodgkin Lymphoma Misdiagnosis

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ABSTRACT

Despite a recent decline, tuberculosis (TB) infection is still a frequent diagnosis in Portugal. Adenosine deaminase (ADA) measurement has become an important tool in the timely diagnosis of this infection. However, ADA elevation in bodily fluids is not pathognomonic of TB infection.

We present the case of a 70-year-old woman, undergoing treatment for pleural TB, diagnosed based on elevated ADA levels in a pleural effusion. Due to worsening symptoms she was readmitted, and the previous diagnosis was reconsidered. Thoracocentesis was repeated and cytometry analysis of the fluid was performed, showing the presence of diffuse large B cell lymphoma (DLBCL).

DLBCL is the most frequently occurring non-Hodgkin lymphoma (NHL). Pleural involvement is rare in the initial stages. ADA elevation >250 U/l should raise suspicion of malignancy, especially in association with markedly elevated LDH levels. The purpose of this case report is to highlight that in the absence of microbiologic or histologic confirmation, a presumptive TB diagnosis should not be lightly made, and alternative diagnoses should be systematically ruled out.

LEARNING POINTS

- Elevated ADA levels are not pathognomonic of TB infection.
- Lymphocytic pleural effusion requires a systematic diagnostic approach.
- Very high levels of ADA should arouse suspicion of lymphoma.

KEYWORDS

Adenosine deaminase, tuberculosis, lymphoma, pleural effusion

CASE DESCRIPTION

A 70-year-old woman presented to the Emergency Department (ED) of our hospital with gradually worsening anorexia, and dyspnoea.

She was in her usual state up to 2 months prior when she developed dyspnoea and anorexia, leading to her first visit to the ED and hospitalization. During the initial evaluation, chest computed tomography (CT) was performed, which showed a large left pleural effusion and minimal right-sided pleural effusion, with no parenchymal abnormalities.

Thoracocentesis yielded a pleural exudate with a high leucocyte count (15.790/mcl) with 67.5% monocytes, and markedly elevated adenosine deaminase (ADA; 269.4 U/l) and LDH (3.590 IU/l) levels.

Pleural biopsy reported a non-specific inflammation of the pleural tissue without malignancy, granulomas or acid-alcohol resistant bacilli. Pleural fluid cultures were negative.

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A presumptive diagnosis of pleural TB was made, based on elevated ADA levels, and empirical therapy was started with isoniazid, rifampicin, ethambutol and pyrazinamide. The patient reported an improvement in her general wellbeing and was discharged.

Over the following 2 months, the patient reported recurring progressing asthenia and anorexia. On the day of readmission, sudden-onset dyspnoea and general malaise developed, motivating a new admission to the ED.

Chest radiography showed an enlargement of the cardiac silhouette and a large-volume right pleural effusion. CT further showed a small left pleural effusion. Both CT and echocardiography showed a circumferential pericardial effusion with no further sonographic signs of tamponade risk. No other lesions besides pleural and pericardial effusions were found on the CT scan.

Blood tests yielded a normal haemogram, with elevated C-reactive protein (88.7 mg/dl) and LDH (335 IU/l) levels with no additional remarkable findings.

Pleural effusion analysis showed an elevated leucocyte count, ADA levels of 203.5 U/l and LDH elevation (1.535 IU/l).

Intravenous methylprednisolone was started at admission due to the pericardial effusion, resulting in rapid improvement of both the pericardial and pleural effusions.

Despite improvement, a small pleural effusion remained visible on chest radiography and a new thoracocentesis was performed during the hospitalization. This time, flow cytometry analysis was requested that identified the presence of anomalous lymphocytes, the immunophenotypic characteristics of which supported the diagnosis of diffuse large B cell lymphoma (DLBCL).

Empirical TB therapy was thus stopped, and the patient was referred to the Haematology department for treatment.

Due to the loss of muscle mass and autonomy, the patient was discharged to a rehabilitation facility to improve functional status before any treatment options were considered.

DISCUSSION

Measurement of ADA has been widely recognized as being a useful tool in the diagnosis of TB due to its high sensitivity and specificity (92% and 90%, respectively) [1]. However, TB is not the only infection, let alone the only disease, that presents with elevated ADA levels [2, 3].

ADA is an essential enzyme in the purine pathway of DNA metabolism and is widely distributed in tissues and bodily fluids, but its main reservoir is lymphoid tissue, and particularly, T lymphocytes [2]. As such, ADA elevation in TB-associated pleural effusions is related to the large number of T cells mediating the inflammatory response to TB infection [4]. On the other hand, infiltration of the pleural space by lymphoma also leads to an increased lymphocyte count and consequent ADA elevation [5].

Despite its undoubted usefulness, the measurement of ADA levels may be misleading as several studies have shown limitations in differentiating some causes of high ADA levels, such as other infections or malignancies [2, 3, 6]. Interpretation of the levels of this marker should therefore take into consideration the clinical findings and other test results, as well as local prevalence rates of the different causes of elevated ADA.

Furthermore, it has been pointed that very high levels of ADA are more suggestive of malignant aetiologies rather than TB. Porcel et al. suggest that an ADA measurement above the cut-off of 250 U/l should raise suspicion of lymphoma rather than TB [7].

The Portuguese incidence of TB infection has seen a steep decline in recent years, with a reduction in the incidence rate from 39.3 (cases per 100,000 habitants) in 2000 to 15.4 in 2018 [8]. On the other hand, the reported incidence rate of non-Hodgkin lymphoma (NHL) in 2010 was 17.1 cases per 100,000 people. Contrary to TB rates, however, the projected incidence rates of NHL are rising [9]. As such, the likelihood of each diagnosis in the setting of a pleural effusion is changing over time.

DLBCL is the most common type of NHL. Usually, in the early stages, it presents without specific symptoms. Approximately a third of patients present only general symptoms, such as fever, weight loss and night sweats [10]. Approximately 25% of NHL cases develop pleural effusion at a certain point of their natural history [11], although this very rarely presents as the original manifestation. DLBCL accounts for approximately 60% of these cases [12, 13].

Cytological analysis of pleural fluid samples yields a positive result in approximately 60% of cases where neoplastic involvement is present, with a reported range of 40–87%. However, it is important to note that this is dependent on the type of malignancy, as for example, lymphomas have a lower cytological detection rate than adenocarcinomas. Obtaining more samples seems to bring little benefit [14].

Flow cytometry analysis can be useful in detecting and characterizing lymphocyte populations in pleural effusions and in conjunction with cytological analysis can reach a positive yield of nearly 100% in cases of malignant effusion [15].

When attempting to acquire a pleural tissue specimen, there are many alternatives, namely blind biopsy, image-guided biopsy, local anaesthetic thoracoscopy (LAT) and video-assisted thoracic surgery (VATS), each with specific advantages and disadvantages. Blind biopsy remains a valid alternative in settings with a high pre-test probability of TB infection as it affects the pleura in a diffuse manner, and as such, allows for a sensitivity of up to 80% [16].

The main advantage of image-guided biopsy over blind biopsy is the obvious ability to accurately biopsy focal pleural thickening and nodules. Each imaging technique (ultrasound, fluoroscopy or CT) will offer its own advantages and drawbacks. VATS remains the gold standard for the diagnosis of malignancies but due to its invasiveness is often only procured in the setting of negative first-line diagnostic tests. LAT can offer a combined therapeutic and diagnostic approach, with the opportunity to directly visualize the pleural cavity and to choose the biopsy site, even allowing for multiple biopsies to be made with a single entry point. Diacon et al. reported a 100% sensitivity for the diagnosis of TB using LAT [16].

In conclusion, when facing a pleural effusion, it is of the utmost importance to have a systematic approach to assessing lymphocytic pleural effusions, particularly in cases lacking more specific clinical presentation or imaging findings, and to refrain from starting empirical antimicrobial therapy in the absence of either microbiological or histopathological evidence of infection in clinically stable patients.

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