Case Report

Diagnostic Dilemma of Antineutrophil Cytoplasmic Antibody Seropositivity in Human Immunodeficiency Virus Infection

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ABSTRACT

We present a case of a 48-year-old male who was diagnosed and treated for Wegener's granulomatosis on the basis of history, clinical features, computed tomography (CT) and antineutrophil cytoplasmic antibodies (ANCA) positivity. The patient initially improved and later on during course of the disease he was found to be human immunodeficiency virus (HIV) seropositive. The potential pitfalls of cANCA in a HIV-infected patient are discussed.
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Key words: Wegener's granulomatosis, HIV, ANCA, Radiology.

INTRODUCTION

Wegener's granulomatosis is a necrotising granulomatous vasculitis involving respiratory tract and kidneys. The available literature suggests that ANCA are highly specific for Wegener's granulomatosis. Clinicians use cytoplasmic pattern of ANCA (cANCA) for serologic confirmation of Wegener's granulomatosis.

CASE REPORT

A 48-year-old male was admitted to hospital with cough, low-grade fever, minimal haemoptysis and progressive dyspnoea for six weeks. He had taken some treatment for nearly three weeks from a private practitioner but no records were available. Repeated sputum smear examinations were negative for *Mycobacterium tuberculosis*. On admission, the haemoglobin was 12 gm/dL, total leukocyte counts (TLC) were 17,900/cmm with 64% neutrophils, platelets 2.5 lakh/cmm^3 and the erythrocyte sedimentation rate (ESR) was 47mm at first hour (Westergren). Serum urea and creatinine levels were 20mg/dL and 1.3mg/dL, respectively. Urinalyses (routine and microscopic) was normal. Chest radiograph and CT of thorax at the time of admission are shown in figures 1 and 2, respectively. Based on chest radiograph and CT of thorax, the patient was put on standard antituberculosis treatment (ATT) empirically and bronchoalveolar lavage (BAL) for cytology and acid-fast bacilli (AFB) was planned. Flexible bronchoscopic examination revealed no abnormality up to the level of sub-segmental bronchi. BAL cytology was non-contributory. Wegener's granulomatosis was considered as next possible differential diagnosis. Subsequently, he was found positive for cANCA by both indirect immunofluorescence and proteinase 3 (PR3) capture assays (quantitative test, kit used- Varelisa™, Phadia GmbH, Freiburg, Germany).

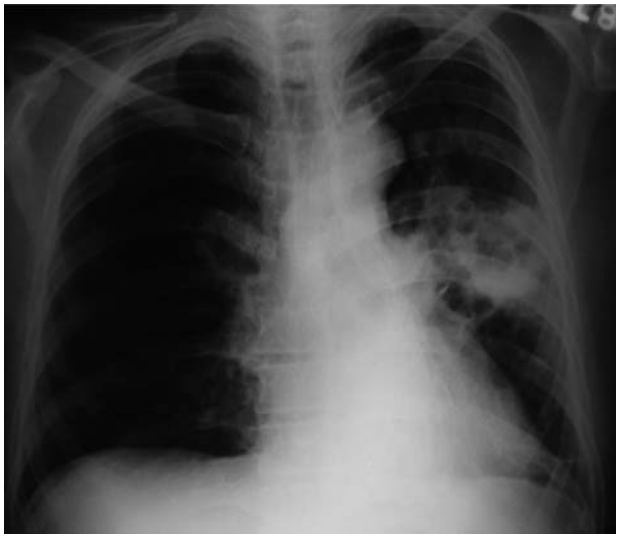

Figure 1. Chest radiograph (postero-anterior view) showing left mid-zone consolidation with multiple cavitations.

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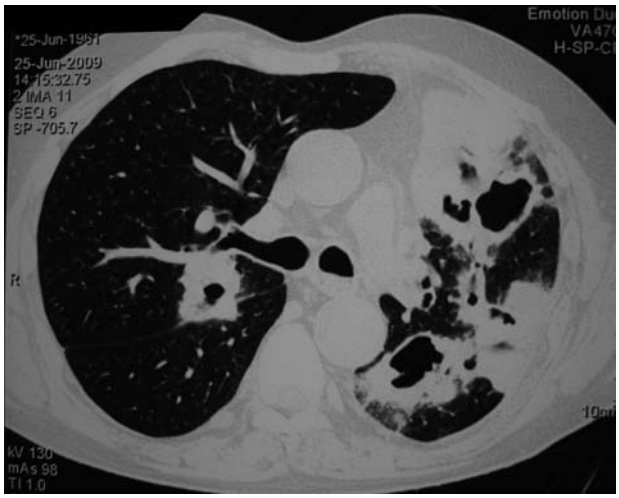

Figure 2. Computed tomography of thorax at level carina showing bilateral (left > right) consolidation with thick-walled cavitating lesions.

Based on abnormalities on CT thorax and laboratory reports of positive cANCA, we raised the diagnosis to Wegener's granulomatosis, and ATT was stopped. He was now treated with cyclophosphamide and prednisolone. The patient improved both clinically as well as radiologically during the hospital stay. The TLC was reduced to 11,300/cmm with 70% neutrophils. He was on regular follow-up and showed further improvement clinically and radiologically (Figure 3). After four-and-a-half months the patient was admitted again with clinical deterioration. At this time, haemoglobin was 11.6 gm/dL, TLC was 7,000/cmm with 88% neutrophils and platelets was 1.78 lakh/cmm^3. Serum urea and creatinine levels were 51mg/dL and 1.2mg/dL, respectively. Sputum for AFB was negative. He was found positive for HIV (confirmed by three different methods) with a CD4 cell count of 09/μL.

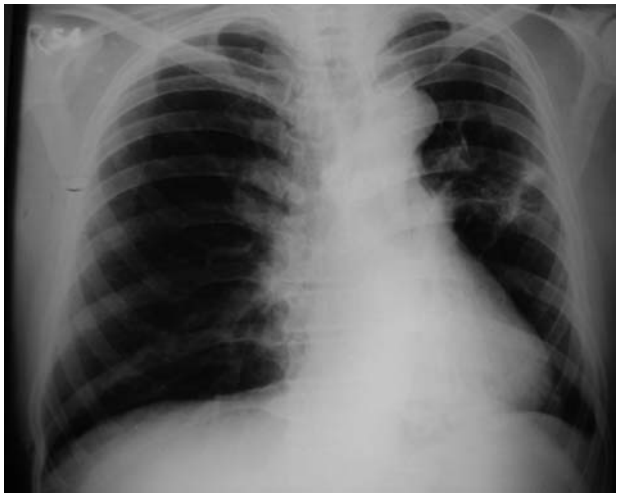

Figure 3. Follow-up chest radiograph (PA view) after three months reveals significant resolution of left mid-zone consolidation.

He was referred to nearest apex hospital for anti-retroviral treatment. After four days, the patient succumbed while on anti-retroviral treatment.

DISCUSSION

The patient either had concurrent HIV and Wegener's granulomatosis or there was a false positivity to ANCA. It is difficult to conclude that our clinical interpretations and subsequent treatment with cyclophosphamide and prednisolone was erroneous.

Antineutrophil cytoplasmic antibodies are immunoglobulin (Ig) G autoantibodies directed against constituents of primary granules of neutrophils and monocytes' lysosomes. Although, numerous antigenic targets have been recognised, the ANCA directed to proteinase 3(PR3) or myeloperoxidase (MPO) are clinically important, whereas the importance of other ANCA remains unknown. The PR3 is the usual target of cANCA. The cANCA have provided clinicians with a serological test that is useful to assist in the diagnosis of Wegener's granulomatosis and few other vasculitides. Further, when positive results from indirect immunofluorescence and enzyme linked immunosorbent assay are combined, specificity for ANCA-associated vasculitides is 99% and sensitivity for Wegener's granulomatosis is 73 percent.[1] When there is a high clinical suspicion, the determination of ANCA is most valuable tool to support the diagnosis of Wegener's granulomatosis (positive predictive value 95%) in the setting of high suspicion.[2]

Search of the literature on ANCA positivity secondary to HIV infection revealed several interesting studies. Savige *et al*[3] found 44 patients (42%) with ANCA on immunofluorescence testing out of 105 HIV-infected patients, including 26 with MPO specificity, whereas Cornely *et al*[4] found 40 ANCA-positive patients (20%) out of 199 HIV-infected patients, 67 of whom revealed an atypical pattern and 33% a pANCA pattern. Cornely *et al*[4] found MPO positivity in only one out of 199 HIV patients (0.5%), whereas Koderisch *et al*[5] found a faint cANCA positivity in 24 out of 29 HIV-infected patients (83%).

The cytopathic effect of HIV on CD4 T-cells and the active autoimmune mechanism play a vital role in the pathogenesis of the infection. The tumour necrosis factor alpha (TNF-α) is an important cytokine produced by the monocyte-macrophage series in HIV infection. This cytokine induces antigens such as PR3 or MPO. Antineutrophil cytoplasmic antibodies are directed against these antigens.[6] So ANCA positivity may be seen in HIV-infected patients. A wide range of vasculitic manifestations have been reported in HIV-infected individuals. Vasculitis has been described in both early in the disease with CD4 counts >500/μL and later in patients with CD4 counts <200/μL.[7]

Granulomatous necrotising vasculitis has also been observed in HIV infection.[8]

In case we consider this as a case of HIV infection and not Wegener's granulomatosis, we need to correlate the clinical features, radiographic and CT findings. The patient had daily treatment (possibly ATT) for about three weeks before being admitted in our hospital and ATT was also continued in our hospital for nearly 10 days for which microscopic diagnosis could not be established. The ANCA positivity made us to believe that the patient had Wegener's granulomatosis and further diagnostic work-up was not pursued.

Selective or limited knowledge as well as premature closure of the diagnostic process, and publication bias on the specificity of ANCA might sometimes lead to erroneous interpretation particularly with a confounding clinical presentation of pulmonary symptomatology, as in the present case. Such treatment may result in a potentially dangerous situation as cytotoxic therapy for Wegener's granulomatosis may well be fatal in acquired immunodeficiency syndrome. Clinicians should be aware of the possibility of a false positive ANCA, particularly in view of the current HIV epidemiology in this region. We conclude that in view of the increasing screening application of ANCA, one should be aware of false-positive results in all clinical presentations. There seems to be a real risk that clinicians may jump to conclusions in cases with a clinical suggestion of Wegener's granulomatosis with cANCA positivity. History taking in ANCA-positive patients should include the risk factors for HIV infection and all cANCA positive patients should under go HIV screening.

A careful work-up including biopsy is required in patients in whom Wegener's granulomatosis is suspected, even when cANCA is found positive. One must be cautious in interpreting a positive ANCA in HIV-infected patients.

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