Netherlands
The Journal of Medicine

CASE REPORT

A therapy resistant vasculitis?

A. Gijzel[1]*, C. Haagsma[2], T. Veneman[1]

Departments of [1]Internal Medicine and [2]Rheumatology, Twenteborg Hospital, 7600 GZ Almelo, the Netherlands, *corresponding author: tel.: +31 (0)546-69 42 69

KEYWORDS

EBV, non-Hodgkin's lymphoma, vasculitis

INTRODUCTION

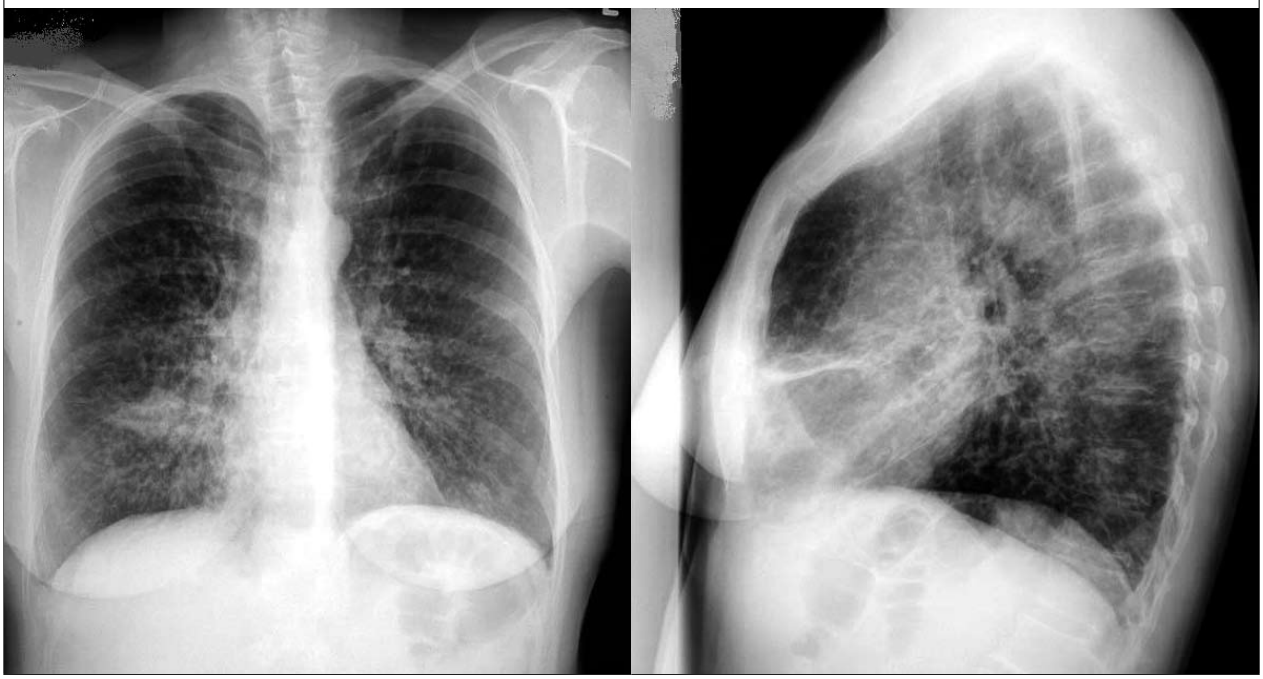
A variety of rheumatic and other autoimmune diseases are treated with immunosuppressive therapy.[1] The therapy often has to be continued for a prolonged period of time, thereby increasing the chance of complications developing and influencing the prognosis of the patient.[1]
Common complications include various forms of organ damage, such as liver failure and bone marrow suppression. In addition, severe (opportunistic) infections and malignancies can occur.[2,3] These complications are frequently accompanied by diagnostic and therapeutic dilemmas mainly due to the atypical course of the disease. In this case, the first occurrence of an Ebstein-Barr virus (EBV)-positive non-Hodgkin's lymphoma during the treatment of Wegener's disease with azathioprine is described.[1-3] Partly because of this extremely rare combination, the diagnostic and therapeutic procedures were complicated.

CASE REPORT

A 60-year-old woman presented to the Emergency Unit because of severe dyspnoea and fever. In the previous two months she complained of progressive cough with production of white sputum, and progressive fatigue. Wegener's disease had been diagnosed in this patient 2½ years earlier, based on c-ANCA and anti-PR3 positive arthritis, pneumonitis and glomerulonephritis, which was in full remission under treatment with prednisone and azathioprine. She had initially been treated with cyclophosphamide, followed by azathioprine and prednisone. The azathioprine had been discontinued one month earlier because of leucopenia and thrombocytopenia.

Physical examination revealed a non-dyspnoeic woman with a body temperature of 39.0°C. She had herpes labialis. Auscultation revealed crackles over both lungs. Liver, spleen and lymph nodes were not palpable.
Laboratory investigation showed a haemoglobin (Hb) of 7.1 mmol/l (7.5-10.0), white blood cell count 4.3 x 10^9/l (4.0-11.0), thrombocyte count 122 x 10^9/l (150-400), erythrocyte sedimentation rate 44 mm/h (<20), C-reactive protein (CRP) 186 mg/l (0-10), sodium 128 mmol/l (135-145), creatinine 97 μmol/l (70-100), slightly elevated γ-glutamyltranspeptidase and transaminase, and a lactate dehydrogenase of 614 U/l (135-225). c-ANCA-IF and anti-PR3 remained negative. Urine analysis revealed no protein or cylinders. The arterial blood gas analysis showed the presence of a respiratory alkalosis with hypoxia.
The chest X-ray showed bilateral diffuse reticulo-nodular abnormalities with a consolidation in the right middle lobe (*figure 1*).
Microbiological investigations remained negative. Cultures of blood and bronchoscopic fluid were negative for *Pneumocystis carinii* pneumonia, cytomegalovirus, tuberculosis, EBV, respiratory viruses, mycoplasma, *Chlamydia* and other micro-organisms. Virus serology did not provide evidence of the presence of an acute viral infection. In addition, the *Legionella* test remained negative. Bronchoscopy revealed the presence of bronchitis.
Under the suspicion of a bacterial infection during immunosuppressive therapy the patient was initially treated with a high dose of cotrimoxazole, pending further investigation. In addition she was treated with valaciclovir because of the suspicion of infection by the herpes virus. Initially these therapeutic measures led to a short clinical improvement with normalisation of her body temperature and CRP. Shortly thereafter, however, her condition deteriorated with complaints of dyspnoea, hypoxia and fever. In the differential diagnosis reactivation of Wegener's disease was considered. In addition, the presence of an opportunistic infection, a second autoimmune disease or

Figure 1. *Chest X-ray of patient on admission*



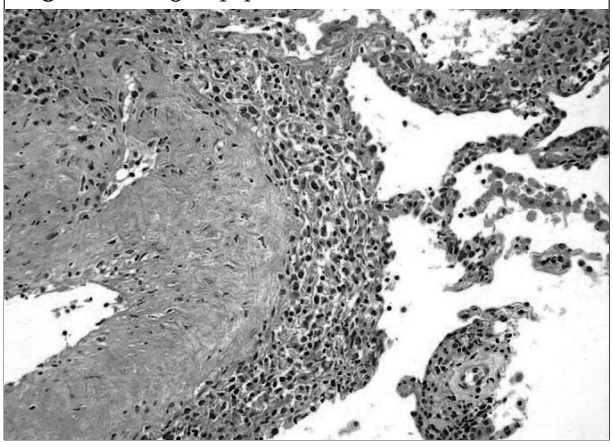
malignancy were all included in the differential diagnosis. Pathological investigation of the transbronchial biopsies showed vasculitis of the smaller to middle-size vessels, without fibrinoid necrosis (*figure 2*). Because cultures and the first serological investigation remained negative, therapy was started with prednisone pulse therapy.

The clinical situation became complicated by melaena, haemodynamic instability and progressive respiratory failure. Gastroscopy revealed an erosive oesophago-gastroduodenitis, which was treated with proton pump inhibition. Because still no clinical improvement was seen after initiation of the prednisone pulse therapy, cyclophosphamide was added, after a bone marrow sample taken from the sternum showed no abnormalities.

On day 18 after admission the patient was admitted to the ICU because of progressive respiratory insufficiency and exhaustion. She was sedated, intubated and mechanically ventilated. At that time she had developed leucopenia, thrombopenia as well as anaemia with a decreasing Hb concentration to 3.0 mmol/l, which was treated with a blood transfusion. In spite of maximal support of the vital functions, the patient died as a consequence of multi-organ failure.

Postmortem investigation revealed diffuse petechiae and haematomas in the skin of the torso and extremities. There was a bilateral pneumonia and bilateral pleural effusions. In addition haemorrhagic lesions based on vasculitis of the small and middle-size arteries were found to be diffuse in the lungs, kidneys, adrenal glands and liver. The liver and spleen were enlarged. A perforation was found in the distal part of the ileum, 6 cm in front of the valvula bauhini. More distal blood clots and blood were seen in the colon and rectum.

Figure 2. *Lung biopsy 10 x HEion*



Cultures taken during autopsy from the lungs and spleen revealed growth of *Staphylococcus aureus*. In several different organs, in particular in the adrenal glands, cytomegalovirus was found. Additional investigation showed groups of atypical cells in various organs. Atypical cell proliferation of lymphoid and plasmacytoid cells was particularly seen around the perforation of the distal ileum, immunohistochemically matching an EBV-positive B-cell non-Hodgkin's lymphoma.

DISCUSSION

Development of EBV-related lymphoproliferative diseases is regularly reported in patients on immunosuppressive therapy after an organ transplant or during treatment

with methotrexate (MTX) because of rheumatic disease.[1-3] Generally it involves B-cell lymphomas but occasionally T-cell lymphomas, which in some instances are detected as early as after six months of therapy. Occasionally the lymphomas show remission after suspension of the immunosuppressive therapy.[4,5] The majority of the documented cases are EBV-related lymphomas during treatment with MTX. We have not been able to find any documentation on lymphomas developing during treatment with azathioprine because of Wegener's disease. The fact that the bone marrow specimen and the haematological parameters normalised after suspension of the azathioprine suggested that the azathioprine had caused the leucopenia and thrombopenia, which had developed in the month prior to admission. At first, on the basis of the clinical presentation in combination with the finding on the chest X-ray, we assumed the presence of an opportunistic infection. Only after microbiological investigation remained negative and supported by the results of transbronchial lung biopsies, therapy with immunosuppressive therapy was initiated. Since there was no clinical improvement, other diagnostic options were considered. Although c-ANCA and anti-PR3 were negative in this previously positive case of Wegener vasculitis recurrence remains a possible diagnosis. One study reported six ANCA-negative relapses out of 13 patients.[6] In another report a patient with vasculitis was presented with recurrent nodules on the chest X-ray without recurrence of anti-PR3 antibodies.[7] Retrospectively perivascular infiltrates with EBV-positive lymphoma cells were found in the transbronchial lung biopsies after additional immunohistochemical testing. A prompt diagnosis of non-Hodgkin's lymphoma could possibly have led to other therapeutic strategies such as treatment with rituximab.[8,9] This case presents an extremely rare combination of diseases, which has not been described previously.

CONCLUSION

Although a relapse of vasculitis is a possibility in the case of a PR3-negative reticulonodular pulmonary infiltrates in a previously c-ANCA and PR3 positive Wegener vasculitis, the differential diagnosis should be extended to a specific search for EBV and associated lymphoreticular malignancy.

REFERENCES

1. Cohen Y, Amir G, Schibi G, Amariglio N, Polliack A. Rapidly progressive diffuse large B-cell lymphoma with initial clinical presentation mimicking seronegative Wegener's granulomatosis. Eur J Haematology 2004;73(2):134-8.
2. Niedobitek G, Mutimer DJ, Williams A, et al. Epstein-Barr virus infection and malignant lymphomas in liver transplant recipients. Int J Cancer 1997;73(4):514-20.
3. Collins MH, Montone KT, Leahy AM, et al. Post-transplant lymphoproliferative disease in children. Pedriatr Transplant 2001;5(4):250-7.
4. Ogata M, Kikuchi H, Ono K, Ohtsuka E, Gamachi A, Kashima K. Spontaneous remission of Epstein Barr virus negative non-Hodgkin lymphoma after withdrawal of cyclosporine in a patient with refractory anemia. Int J Hematol 2004;79(2):161-4.
5. Hurwitz M, Desai DM, Cox KL, Berquist WE, Esquivel CO, Millan M. Complete immunosuppressive withdrawal as a uniform approach to post-transplant lymphoproliferative disease in pediatric liver transplantation. Pediatr Transplant 2004;8(3):267-72.
6. Girard T, Mahr A, Noel L-H, et al. Are antineutrophil cytoplasmatic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. Rheumatology 2001;40:147-151.
7. Taniguchi H, Honda R, Adachi Y, Abo H, Noto H, Izumi S. A case of Wegener's granulomatosis without PR3-ANCA at relapse. Nihon Kokyuki Gakkai Zasshi 2005;43 (9):547-51.
8. Rastetter W, Molina A, White CA. Rituximab: Expanding role in therapy for lymphomas and autoimmune diseases. Annu Rev Med 2004;55:477-503.
9. Blaes AH, Peterson BA, Bartlett N, Dunn DL, Morrison VA. Rituximab therapy is effective for posttransplant lymph proliferative disorders after solid organ transplantation: results of a phase II trial. Cancer 2005;104(8):1661-7.