CASE REPORT

An ICU patient with spots and a peculiar pneumonia

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SUMMARY

This is the first report of varicella zoster virus (VZV) pneumonia in an adult patient treated with rituximab because of autoimmune haemolytic anaemia and it illustrates that a VZV infection should be considered when an immunocompromised patient develops pulmonary symptoms, even in the absence of cutaneous lesions. It also depicts the importance of performing varicella serology in patients receiving multiple immunosuppressive agents.

BACKGROUND

This case emphasises the importance of performing varicella serology in patients prior to receiving multiple immunosuppressive agents and considering

varicella zoster virus (VZV) pneumonia in such patients early on, even though skin lesions are absent.

Primary infection with VZV causes a diffuse vesicular rash referred to as varicella (chicken pox). Reactivation of latent VZV results in a localised skin infection named herpes zoster (shingles). In immunocompromised patients, disseminated zoster can develop.

Although fewer than 5% of VZV infections occur in adults and only 0.1% develop in immunocompromised patients, these groups have a significantly higher morbidity and death rate. Immunocompromised patients account for as many as 25% of varicella-related deaths.¹ Pneumonia is the most common serious complication with a

Table 1 Laboratory examination on admission to the intensive care unit

Laboratory test	Value	Reference value
Hemoglobin	5.4 mmol/L	6.9 to 10.0 mmol/L
Mean cell volume	104 fl	82 to 98 fl
Thrombocytes	132 x10 ⁹ /L	150 to 350 x10 ⁹ /L
Leucocyte count	1.9 x10 ⁹ /L	4.0 to 10.0 x10 ⁹ /L
– basophil granulocytes	0.0 x10 ⁹ /L	<–0.1 x10 ⁹ /L
– eosinophil granulocyte	0.0 x10 ⁹ /L	<–0.3 x10 ⁹ /L
– neutrophil granulocyte	1.7 x10 ⁹ /L	1.3 to 5.7 x10 ⁹ /L
– lymphocytes	0.1 x10 ⁹ /L	0.8 to 3.7 x10 ⁹ /L
– monocytes	0.1 x10 ⁹ /L	0.2 to 0.9 x10 ⁹ /L
– % immature granulocytes	3 %	
– erythroblasts /100 leukocytes	6	
Reticulocytes	141 x10 ⁹ /L	10 to 70 x10 ⁹ /L
C-reactive protein	77 mg/L	<10 mg/L
Sodium	141 mmol/L	135 to 145 mmol/L
Potassium	4.5 mmol/L	3.5 to 5.0 mmol/L
Urea	15 mmol/L	2.9 to 7.5 mmol/L
Creatinin	128 µmol/L	62 to 106 µmol/L
Gamma-glutamyl transferase	222 U/L	<35 U/L
Alkaline phosphatase	93 U/L	35 to 120 U/L
Alanine aminotransferase	50 U/L	<45 U/L
Aspartate aminotransferase	40 U/L	<40 U/L
Lactate dehydrogenase	600 U/l	<220 U/l
Bilirubin	23 µmol/L	<17 µmol/L
Conjugated bilirubin	11 µmol/L	<5 µmol/L
Haptoglobin	<0.10 g/L	0.3 to 2.0 g/L
Lactate	4.4 mmol/L	0.5 to 2.2 mmol/L
Albumin	27 g/L	35 to 55 g/L
pH°	7.49	7.35 to 7.45
pCO2°	3.0 kPa	4.7 to 6.4 kPa
pO2°*	9.6 kPa	10.0 to 13.3 kPa
Bicarbonate°	17.0 mmol/L	22 to 29 mmol/L
Base excess	–5.1 mmol/L	–3 to +3 mmol/L

° arterial

* with 2 litres supplemental oxygen.

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Figure 1 (A) Chest x-ray showing a small infiltrate in the right lower lobe. (B and C) Skin lesions on day 4: papules and vesicles, not following a dermatome. (D) Chest x-ray on the fourth day after admission showing bilateral interstitial attenuation.

death rate of 10–20% and 50% in patients who require mechanical ventilation.²

In VZV pneumonia, respiratory symptoms usually start 3–5 days after the onset of blisters, except in about 10% where respiratory symptoms precede cutaneous manifestations.³ Chest radiographs show an interstitial or micronodular pattern.⁴ Prompt administration of intravenous acyclovir improves outcome.^{5,6}

We describe a patient treated with rituximab, on top of other immunosuppressants, for autoimmune haemolytic anaemia (AIHA) who developed a severe VZV pneumonia. Up until now, few cases of VZV infection during rituximab treatment were reported and to our knowledge, no case of VZV pneumonia in an adult treated with rituximab because of AIHA has been described.^{7–11}

CASE PRESENTATION

A 74-year-old man presented with coughing, dyspnoea, a sore throat, palpitations, nausea and loss of appetite since 1 week. His medical history revealed diabetes mellitus type II and AIHA with both aspecific warm and cold autoantibodies (anti-IgG and anti-complement). For the AIHA he had been treated with azathioprine for several years and with additionally 20 mg/day prednisone for several months. Since 2 weeks he had been treated with weekly rituximab injections to reduce the long-term prednisone toxicity.

INVESTIGATIONS

Upon physical examination, he had a temperature of 39.6°C, his blood pressure was 130/70 mm Hg, he was tachycardiac (100 beats/min, irregular rhythm) and tachypnoeic (30 breaths/min). Laboratory results are shown in table 1.

A chest x-ray (CXR) showed a small infiltrate in the right lower lobe (figure 1A). The fourth day after admission, patient became more dyspnoeic and tachypnoeic and developed skin lesions on his face and trunk (figure 1B and C). Bilateral interstitial attenuation was seen on a second CXR (figure 1D).

DIFFERENTIAL DIAGNOSIS

Before development of the skin lesions, differential diagnosis included a rituximab-induced interstitial pneumonia and a severe community-acquired pneumonia (CAP) for which moxifloxacin was started.

TREATMENT

The patient was transferred to the intensive care unit (ICU) and treatment with acyclovir (750 mg intravenous twice daily) was initiated under suspicion of a VZV pneumonia. The azathioprine and rituximab were discontinued. Because of chronic steroid treatment, a hydrocortisone stress scheme was started (hydrocortisone 100 mg three times a day).

OUTCOME AND FOLLOW-UP

Over the night, respiratory insufficiency developed and mechanical ventilation was started after tracheal intubation. A high-resolution CT (HR-CT) scan showed interstitial lung disease

Figure 2 High-resolution CT revealing interstitial lung disease with bronchial wall thickening, ground glass appearance and 'crazy paving' pattern and a consolidate in the right middle lobe.

Figure 3 Microscopy of bronchoalveolar lavage fluid, showing a relative lymphocytosis.

(figure 2). Microscopy of material obtained by bronchoalveolar lavage (BAL) revealed a relative lymphocytosis (figure 3).

PCR of both the BAL fluid and fluid obtained from the skin vesicles were positive for VZV.

Noteworthy are the ECG abnormalities (figure 4). Creatine kinase (CK) levels were not elevated.

The patient recovered well and after 5 days he could be extubated and discharged from the ICU and hospital after respectively 9 and 17 days.

DISCUSSION

We described a case of VZV pneumonia in an adult patient treated with rituximab since 2 weeks because of AIHA. Considering the patient's age and the fact that he had not had any contact with children with VZV prior to the development of symptoms, disseminated zoster is more likely than a primary VZV infection, but unfortunately we could not confirm this. His serostatus was unknown and it was not possible to test it anymore, since the patient died of a sudden deterioration of his AIHA shortly after the described admission and there was no serum stored to test for IgG, retrospectively. We were also unable to find out if he had chickenpox in his youth although this seems likely since seroprevalence for VZV in the Netherlands is almost 100% at this age.¹²

Only a few cases of VZV pneumonia during rituximab treatment have been reported previously and this is the first report of VZV pneumonia in an adult during rituximab treatment for

AIHA.^{7–11} Rituximab is an anti-CD20 monoclonal antibody, which is successfully used in the treatment of B-cell neoplasm and several autoimmune disorders, such as rheumatoid arthritis and AIHA, unresponsive to first-line therapies. Diffuse parenchymal lung disease owing to an inflammatory reaction has been reported in 0.03–8% of the patients treated with rituximab.¹³ Most of these patients present with interstitial lung disease and respond well to corticosteroid therapy.

VZV infection during rituximab use is rare and the effect of rituximab on the risk of (viral) infection remains controversial. Since rituximab causes depletion of B lymphocytes and has no effect on T-cell immunity, an increased susceptibility for mainly bacterial infections should be expected.⁷ However, Aksoy and Habicht^{7–9} both reported increased incidences of viral infections in patients treated with rituximab.

Compared with cases described in the literature, the VZV infection occurred relatively early after the start of rituximab. There is one other report of VZV reactivation within 2 weeks after administration of the first rituximab dose.⁸

It remains uncertain whether the development of severe disseminated VZV infection in our patient was the consequence of the recent commencement of rituximab or if it was the result of his total burden of immunosuppressive medication.

Unlike advised in the Dutch Varicella guideline, VZV serology was not tested in this patient before starting treatment with a combination of three immunosuppressive drugs.¹⁴ Since the varicella vaccine is an attenuated live virus preparation, it is contra-indicated for patients receiving immunosuppressive medication. Prophylactic administration of varicella zoster immune globulin or acyclovir might be an alternative in immunosuppressed patients.

In our patient, there was a delay in starting antiviral therapy. Initially, a severe CAP or interstitial lung disease caused by rituximab were considered. It was not until skin lesions developed and respiratory symptoms increased, that VZV pneumonia was considered.

Because of chronic glucocorticoid use, the patient was treated with adjunctive steroids in a stress dose. It is possible that this had a beneficial effect on the varicella pneumonia.¹⁵

Interestingly, this patient had a remarkable tachycardia during his stay on the ICU. His ECG abnormalities could have been a symptom of VZV myocarditis, which was first described in 1953.¹⁶ A large spectrum of dysrhythmias in varicella myocarditis have been described, such as supraventricular tachycardia with aberrant conduction, ventricular tachycardia, ventricular fibrillation or ST elevations and inverted T waves.^{17–19} In general, ECGs in myocarditis show ventricular dysrhythmias or 'heart block', or

Figure 4 ECG showing a combination of a sinus rhythm and an atrioventricular junctional tachycardia (25 mm/s, 10 mm/mV, 100 Hz).

can demonstrate signs of acute myocardial infarction or pericarditis.²⁰ Unfortunately, in this case, no echocardiography was performed and no troponin serum level was determined. This makes it impossible to determine if the patient in fact suffered from myocarditis.

Learning points

- ▶ It is strongly advised to perform varicella serology in patients before starting treatment with a combination of immunosuppressive agents.
- ▶ Even in the absence of the characteristic cutaneous lesions, varicella zoster virus (VZV) infection should be considered in immunocompromised patients.²¹
- ▶ VZV pneumonia is the most common severe complication of VZV infection in adults.
- ▶ The mortality of VZV pneumonia is high, even despite prompt diagnosis and antiviral therapy.

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REFERENCES

- 1 Straus SE, Ostrove JM, Inchauspe G, *et al.* NIH conference. Varicella-zoster virus infections. Biology, natural history, treatment, and prevention. *Ann Intern Med* 1988;108:221–37.
- 2 Feldman S. Varicella-zoster virus pneumonitis. *Chest* 1994;106(Suppl):22S–7S.
- 3 Chiner E, Ballester I, Betloch I, *et al.* Varicella-zoster virus pneumonia in an adult population: has mortality decreased? *Scand J Infect Dis* 2010;42:215–21.
- 4 de la Pena L, Izaguirre D, Aguirrebengoa K, *et al.* Varicella pneumonia in the adult: study of 22 cases. *Enferm Infecc Microbiol Clin* 2000;18:493–5.
- 5 Haake DA, Zakowski PC, Haake DL, *et al.* Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. *Rev Infect Dis* 1990;12:788–98.
- 6 Wilkins EG, Leen CL, McKendrick MW, *et al.* Management of chickenpox in the adult. A review prepared for the UK advisory group on chickenpox on behalf of the British Society for the study of infection. *J Infect* 1998;36 (Suppl 1):49–58.
- 7 Aksoy S, Harputluoglu H, Kilickap S, *et al.* Rituximab-related viral infections in lymphoma patients. *Leuk Lymphoma* 2007;48:1307–12.
- 8 Tsuda M, Moritoki Y, Lian ZX, *et al.* Biochemical and immunologic effects of rituximab in primary biliary cirrhosis patients with an incomplete response to ursodeoxycholic acid. *Hepatology* 2012;55:512–21.
- 9 Habicht A, Broker V, Blume C, *et al.* Increase of infectious complications in ABO-incompatible kidney transplant recipients—a single centre experience. *Nephrol Dial Transplant* 2011;26:4124–31.
- 10 Kato H, Yamamoto K, Matsuo K, *et al.* Clinical impact and predisposing factors of delayed-onset neutropenia after autologous hematopoietic stem-cell transplantation for B-cell non-Hodgkin lymphoma: association with an incremental risk of infectious events. *Ann Oncol* 2010;21:1699–705.
- 11 Nagel A, Podstawa E, Eickmann M, *et al.* Rituximab mediates a strong elevation of B-cell-activating factor associated with increased pathogen-specific IgG but not autoantibodies in pemphigus vulgaris. *J Invest Dermatol* 2009;129:2202–10.
- 12 de Melker H, Berbers G, Hahne S, *et al.* The epidemiology of varicella and herpes zoster in the Netherlands: implications for varicella zoster virus vaccination. *Vaccine* 2006;24:3946–52.
- 13 Ram R, Ben-Bassat I, Shpilberg O, *et al.* The late adverse events of rituximab therapy—rare but there! *Leuk Lymphoma* 2009;50:1083–95.
- 14 Dutch Society for Medical Microbiology. Central Organ Accompaniment (CBO) guideline Varicella 2010. <http://www.diliguide.nl/document/1337/varicella.html> (accessed 14 Mar 2013).
- 15 Mer M, Richards GA. Corticosteroids in life-threatening varicella pneumonia. *Chest* 1998;114:426–31.
- 16 Hackel DB. Myocarditis in association with varicella. *Am J Pathol* 1953;29:369–79.
- 17 Mahdi A, Anderson S, Carley S, *et al.* Spotting the complex tachycardia. *Emerg Med J* 2010;27:239–41.
- 18 Dennison P, Zaremba E. Varicella zoster induced cardiac dysfunction: a case report. *Emerg Med J* 2007;24:682–3.
- 19 Alter P, Grimm W, Maisch B. Varicella myocarditis in an adult. *Heart* 2001;85:E2.
- 20 Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388–98.
- 21 Gregorakos L, Myrianthefs P, Markou N, *et al.* Severity of illness and outcome in adult patients with primary varicella pneumonia. *Respiration* 2002;69:330–4.

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