treatment and at the same time for OAT is not an unusual occurrence considering the association between cancer and some immunologic diseases with thromboembolic complications. In order to treat such patients properly, it is therefore important to be aware of these pharmacologic interactions that seem to differ with respect to the oral anticoagulant prescribed.

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References

1. Italian Federation of Anticoagulation Clinics. A guide to Oral Anticoagulant Therapy. Haemostasis 1998; 28(Suppl 1):22-4.
2. Advani R, Warnke R, Sikic BI, Horning S. Treatment of angioimmunoblastic T-cell lymphoma with cyclosporin. Ann Oncol 1997; 8:601-3.
3. Snyder DS. Interaction between cyclosporine and warfarin. Ann Intern Med 1988; 108:311.
4. Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 1999; 353:717-9.
5. Campistol JM, Maragall D, Andreu J. Interaction between cyclosporin A and sintrom. Nephron 1989; 53:291-2.

Fatal visceral varicella-zoster infection following rituximab and chemotherapy treatment in a patient with follicular lymphoma

Infections during rituximab therapy are mostly bacterial, minor and usually affect the respiratory tract. Viral infections are less common and serious complications are rare. We report the first case of visceral varicella-zoster infection in a patient with follicular lymphoma after rituximab and chemotherapy treatment.

Sir,

Rituximab is a human immunoglobulin (Ig) with variable regions isolated from a murine anti-CD20 monoclonal antibody.[1-4] It specifically reacts with CD20 antigen on B-cells mediating complement-dependent lysis, antibody-dependent cytotoxicity and apoptosis.[1,3] As monotherapy in relapsed or refractory low-grade NHL an overall 50% response rate has been reported.[1,2] Most adverse events are mild and related to infussion.[1-4] Viral infections during treatment have been seldom reported. We report the first case, to our knowledge, of fatal visceral varicella-zoster virus (VZV) infection in a patient after administration of rituximab and chemotherapy.

A 53-year old female with follicular NHL (stage IV B) was treated with five courses of CHOP achieving partial response. She then received intensive chemotherapy with PBSC support obtaining a complete response. One year later, relapse was observed in peripheral blood, bone marrow and spleen. Fludarabine treatment was started but she received only two cycles because of bad tolerance. Finally, she received 4 doses of rituximab with 6 courses of CVP chemotherapy combination achieving partial response. One week later, the patient was admitted to our hospital with abdominal pain and vomiting. Physical examination revealed a tender abdomen. Blood count only showed thrombocytopenia (40×10^9/L). Amylase, renal and liver function tests, chest and abdominal radiography were normal. An abdominal sonography showed splenomegaly of 15 cm. Omeprazol and analgesia were started but the patient worsened and developed paralytic ileus. Gastroduodenoscopy, abdominal CT scan and finally laparotomy were performed, but did not reveal any pathology. One day after surgery, the patient developed decreased consciousness with tonic movements and DFH treatment was started. No metabolic causes were found. Neurologic examination and brain CT scan were normal. An electroencephalogram revealed focal temporal lobe activity and cerebrospinal fluid (CSF) had only high protein levels (1.01 g/L). CSF cultures were negative.

On the 7th hospital day, she developed a generalized papulo-vesicular rash and acyclovir (10 mg/kg/8h) was initiated. VZV direct fluorescence assay and culture were positive in vesicular fluid. Twelve hours later, she had fever, jaundice, dyspnea and oliguria. Laboratory findings revealed bilirubin 63.2 µmol/L, ALT 2,055 U/L, AST 1,780 U/L, prothrombin time 45 sec and creatinine 354 µmol/L. A CT scan showed pneumonitis with pleural effusion, necrotic hepatomegaly, splenomegaly, ascites, and pancreatic and renal edema. Cytopathic changes suggestive of herpes virus infection were observed in pleural mesothelial cells (Figure 1). Multiorgan failure caused by VZV infection was diagnosed. Despite intensive treatment the patient died. An autopsy was not performed.

VZV infection is an important cause of morbidity in hematologic patients.[5-9] It generally presents as dermatomal reactivation of latent virus.[5,6] Nevertheless, visceral dissemination can occur in highly immunosuppressed populations.[5-9] with near 50% mortality.[6] It is often preceded by cutaneous manifestations so the diagnosis is easy suspected.[7] However, it can precede typical rash by as much as 3 weeks[6] or even be present in the absence of skin lesion.[7] Visceral VZV infection often presents as poorly localized abdominal pain and evolving pancreatitis, hepatitis, paralytic ileus[6-8] or even aseptic meningoencephalitis.[9] Pneumonitis and hepatic failure are the most important causes of mortality.[6-8] However, visceral VZV dissemination is a rare complication during chemotherapy courses or even more than one year following transplantation.[5,8,10] Our patient showed VZV IgG in pretransplantation studies and it is probable that VZV reactivation was mainly related to cellular immunity impairment by lymphoma, fludarabine and corticosteroid treatment. Nevertheless, it has been reported that most rituximab patients have normal Ig levels[2,3]

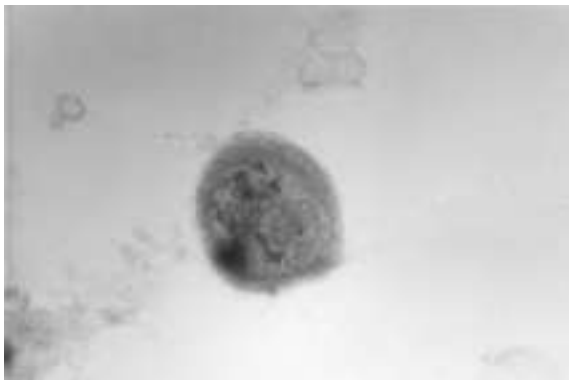

Figure 1. Mesothelial cell with cytopathic changes suggestives of herpes virus infection.

while our patient had low IgG (1.76 g/L) and IgA (0.28 g/L). We could speculate that humoral dysfunction related to rituximab therapy could have caused loss neutralization of free viral particles by specific antibodies, facilitating initial dissemination of the VZV but this hypothesis needs to be investigated further.

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References

1. Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997; 90:2188-95.
2. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16:2825-33.
3. Czuczman MS, Grillo-López AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999; 17:268-76.
4. Coiffer B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92: 1927-32.
5. Schuchter ML, Wingard RJ, Piantadosi S, Burns WH, Santos GW, Saral R. Herpes zoster infection after autologous bone marrow transplantation. Blood 1989; 74:1424-7.
6. David DS, Tegtmeier BR, O'Donnel MR, Paz IB, McCarty TM. Visceral varicella-zoster after bone marrow transplantation: report of a case series and review of the literature. Am J Gastroenterol 1998; 93:810-3.
7. Rogers SY, Irving W, Harris A, Russell NH. Visceral varicella zoster infection after bone marrow transplantation without skin involvement and the use of PCR for diagnosis. Bone Marrow Transplant 1995; 15:805-7.
8. Stemmer SM, Kinsman K, Tellschow S, Jones RB. Fatal noncutaneous visceral infection with varicella-zoster virus in a patient with lymphoma after autologous bone marrow transplantation. Clin Infect Dis 1993; 16:497-9.
9. Han CS, Miller W, Haake R, Weisdorf D. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. Bone Marrow Transplant 1994; 13:277-83.
10. Roitt I. Essential Immunology. 9th ed. Oxford: Blackwell Science Ltd; 1997.

Cyclosporine treatment of acquired hemophilia due to factor VIII antibodies

Acquired hemophilia, caused by autoantibodies against coagulation factor VIII, is usually treated with steroids, cyclophosphamide, intravenous gammaglobulins and sporadically other drugs. We describe the case of a patient in whom the common therapeutic choice was unsuccessful, but cyclosporine proved to be effective.

Sir,

A 56-year old man with chronic obstructive pulmonary disease was admitted because of hemoptysis. There was no evidence of malignancy, tuberculosis or autoimmune disorders. The patient did not take any new drug before admission. Routine coagulation tests showed repeatedly a prolongation of the activated partial thromboplastin time (to 63.7 sec, upper normal value 37 sec). This was due to a decrease of factor VIII:C to 0.04 IU/mL with an antibody level against factor VIII of 40 Bethesda units/mL. An acquired von Willebrand syndrome was excluded (vWF:Ag of 2.38 IU/mL, vWF:Rco of 1.23 IU/mL). Treatment during 3 months with prednisone (initially 1 mg/kg/day) and cyclophosphamide 50 mg p.o. daily, followed by i.v. gammaglobulins (0.4 g/kg/day for 5 days) had no influence on the presence of the antibodies. Later on a subcutaneous hemorrhage in the left arm and bleeding in the sural muscles of the right leg occurred. During that period recombinant activated factor VII was successfully administered. After initiation of cyclosporin, the antibodies against factor VIII progressively decreased and finally disappeared. The treatment was stopped after eight months. The coagulation tests remained normal. Spontaneously acquired antibodies against factor VIII are infrequent. They peak in the third and seventh decades.[1] Intramuscular bleeds are the most common hemorrhagic manifestation. The major cause of acquired antibodies against factor VIII, excluding hemophilia, are autoimmune disorders,