min-K dependent proteins, revealed that the affected amino acid was highly conserved, indicating an important structural or functional role.

The search for other established thrombophilic genetic risk factors such as protein S and antithrombin deficiency, factor V Leiden, methylene tetrahydrofolate reductase C677T variant, and prothrombin G20210A variant revealed that only one patient was heterozygous for the prothrombin variant (Figure 1). Family analysis revealed that individuals with the same mutation responsible for PC deficiency and prothrombin variant, had no clinical thrombosis. These data show that thrombosis can be the result of multiple acquired and genetic factors interacting with a consequent synergistic effect, possibly, including factors which still remain unknown.

In each family the deficiency cosegregates with the mutation (Table 1), indicating that the defect is the likely cause of PC deficiency in these patients.

Our results corroborate that recurrent mutations are very frequent in PC deficiency, since three of our identified mutations were previously described in other countries and two of them involved the hypermutable region of CPG dinucleotides.

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Key words

Protein C, mutation, thrombosis.

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Oral anticoagulants and cyclosporin A

Cyclosporin A and oral anticoagulants have pharmacologic interactions. In this letter we report a case of angioimmunoblastic T-cell lymphoma with a concomitant deep venous thrombosis in which a negative interaction between warfarin and cyclosporin A was observed. The introduction of cyclosporin A required a larger dose of warfarin in order to reach the therapeutic level.

Sir,

A number of drugs can influence both cyclosporin A (CsA) blood levels and course of the oral anticoagulant treatment (OAT) with a synergistic or antagonistic effect.[1]

Few observations exist about the interaction between CsA and oral anticoagulants (OAs). We report here a case of a 65-year old woman who was given CsA while receiving warfarin for venous thromboembolism. In August 1996 a diagnosis of angioimmunoblastic T-cell lymphoma was made and six courses of standard CHOP regimen were given. In November 1996 while still on chemotherapy, the patient developed a deep vein thrombosis (DVT) of the left leg. Low molecular weight heparin was given for two months and DVT regressed. In February 1997 a CT scan of the abdomen showed an asymptomatic vena cava thrombosis spread from the iliac bifurcation to the renal veins and long-term warfarin therapy was started. In October 1997, because of a lymphoma relapse, CsA was introduced at the dose of 300 mg p.o. bid, in order to control the malignant T-cell proliferation as suggested by Advani *et al*.[2] After the beginning of CsA therapy, INR decreased about 40% in several repeated controls, and a larger dose of warfarin had to be administered (from 18.75 mg to 27.50 mg/week, progressively). Thereafter, for a given dose of warfarin, when CsA blood levels remained within the therapeutic range the INR values became stable with the same OA dose. When OAT was withdrawn, CsA blood levels remained unchanged.

To our knowledge, there are only two reports about interactions between CsA and OAs. In the first[3] the patient was receiving warfarin and phenoarbital as well, a drug known to enhance the activity of cytochrome P450[4] and consequently to reduce the pharmacologic effect of both CsA and warfarin. Because of this negative interaction, the dosage of both CsA and warfarin had to be increased. This is at variance with our case in which only the dose of warfarin had to be modified, and the difference can be ascribed to the concomitant use of phenobarbital. In the second report[5] the patient was on acenocoumarol and CsA displayed a potentiating effect of this OA, thus making it necessary to reduce the dosages of both CsA and OA. The reason for this opposite behavior (positive interaction) cannot be explained by the different half-lives: 10 hours for acenocoumarol and 36 hours for warfarin. A different metabolism of acenocoumarol could be assumed with regard to the hydroxylating action of cytochrome P450.[4]

A clinical setting in which there is indication for CsA

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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Key words
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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]