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LETTER TO THE EDITOR

Severe immunosuppression in inflammatory bowel disease: opening the floodgates to opportunists?

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Dear editor:

Ulcerative colitis is a primarily non-infectious, chronic inflammatory bowel disease that typically affects the rectum and may involve the whole colon in an uninterrupted pattern. The disease has a high impact on the patients' health-related quality of life and is prone to repetitive hospitalisation. Therapeutic options primarily include lifestyle alterations, medical management and surgical interventions. Medical as well as surgical therapy may be associated with life-threatening complications, which may require intensive care unit (ICU) admission. Here, we report on a female patient suffering from ulcerative colitis, whose medical therapy was complicated by toxic megacolon, and later on pulmonary aspergillosis and disseminated herpes zoster.

A 55-year old woman with ulcerative colitis suffered from purulent haemorrhagic diarrhoea and weight loss of 9 kg within 2 weeks and was treated in a community general hospital for 6 weeks. Azathioprine (2.5 mg kg^{-1} d^{-1} p.o.) was administered for a total of 15 days and had been discontinued due to severe leukopenia. At that time, the patient had a high erythrocyte thiopurine methyl thiopurine methyltransferase (TPMT) activity (38 nmol h^{-1} $g_{Hb}{}^{-1}$; normal >23, intermediate 10–23, low <10 nmol h^{-1} $g_{Hb}{}^{-1}$), which represents the detoxifyfing enzyme for azathioprine. In addition, TPMT genotyping was performed and confirmed the absence of clinically relevant enzyme polymorphisms. Furthermore, toxic 6-thioguanine nucleotides (6-TGN) were undetectable in the patient's blood.

Persistent bowel inflammation was treated with high doses of topical and systemic corticosteroids (prednisolone up to 2 mg kg^{-1} per day) and intravenous cyclosporine (3 mg kg^{-1} as continuous infusion over 24 h) in combination with antimicrobial therapy. Cyclosporine was discontinued after 6 days as leukopenia deteriorated, and subsequent immunomodulatory therapy consisted of mesalazine and regressive doses of prednisolone.

At transferal to our university hospital, the patient presented the full clinical picture of toxic megacolon, which required emergency subtotal colectomy, blind closure of the rectum and percutaneous ileostomy. Following surgery, the patient was transferred to the intermediate care unit and treated with antimicrobial therapy (cefuroxime and metronidazole) and moderate doses of corticosteroids (prednisolone 1 mg kg^{-1} per day). On postoperative day 3, she developed acute cholecystitis, which required urgent cholecystectomy and escalation of antimicrobial therapy (meropenem and vancomycin). Throughout the early clinical course, the patient remained leukopenic with white blood cell counts between 950 and 2,840 cells per microliter. Fractional lymphocyte count persisted below 10%. Filgrastim treatment (recombinant-methionyl human granulocyte colony-stimulating factor; r-metHuG-CSF;

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$30{\cdot}10^6$ U per day) was initiated and leukopenia (but not lymphopenia) dissolved. On postoperative day 6, she developed septic shock caused by biliary peritonitis due to leakage from an aberrant bile duct. Following closure of the leakage, the patient was transferred to the surgical ICU, where haemodynamic stability could only be maintained with high doses of norepinephrine (0.3 $\mu g\ kg^{-1}\ min^{-1}$) in combination with arginine vasopressin (0.025 $U\ min^{-1}$). After initial stabilisation and weaning from mechanical ventilation, severe respiratory failure requiring prone positioning ensued. Diagnostic bronchoscopy revealed mucosal plaques suspective of pulmonary aspergillosis, and intravenous voriconazole (6 $mg\ kg^{-1}$ every 12 h) was started. The diagnosis was confirmed by isolation of aspergillus fumigatus in bronchoalveolar lavage fluid. The following days were characterized by persistent septic shock and multiple organ failure requiring mechanical ventilation and continuous renal replacement therapy. On day 25 of ICU stay, the patient presented a homogenous, livid, macular exanthema with implied central vesiculation covering the trunk, limbs and visible parts of the intestinal serosa. The differential diagnoses of the consultant dermatologist included virus exanthema, vasculitis or drug eruption from antimicrobial therapy. Within 48 h, the skin rash progressed to scattered, greyish, fragile vesicles with erythemateous base, which rapidly became pustular, incrusted and haemorrhagic. Rapid histological section revealed intraepidermal vesicles with acantholysis and balloon cells reflecting profound intracellular oedema. At this stage, the clinical diagnosis of disseminated herpes zoster was posed, and intravenous treatment with high doses of acyclovir (10 $mg\ kg^{-1}$ every 8 h) was immediately started. The clinical diagnosis was confirmed by isolation of varicella zoster virus (VZV) within the efflorescences and VZV desoxyribonucleid acid in blood samples and ascites specimen. VZV polymerase chain reaction performed every second day revealed positive viraemia until ICU day 46 at a detection limit of 200 copies per milliliter. Intestinal VZV infection was associated with progressive bowel paralysis requiring parenteral nutrition. Throughout the ICU stay, multiple organ failure persisted including acute respiratory distress syndrome, acute renal failure, liver failure and non-occlusive mesenterial ischaemia, resulting in death of the patient on ICU day 49.

The present patient suffering from ulcerative colitis experienced severe drug-related immunosuppression resulting in life-threatening bacterial (toxic megacolon), fungal (invasive aspergillosis) and viral (disseminated herpes zoster) infections.

Usual maintenance treatment of ulcerative colitis consists of oral 5-amino salicylates. In case of exacerbated inflammation, pulsed high doses of steroids are considered useful, and azathioprine may be added to maintain remission. Whereas moderate leukopenia is a common, dose-dependent finding during treatment with azathioprine, severe leukopenia and infection with opportunistic microbes is only reported in 1:100 to 1:1000 of non-transplant patients. Notably, about 10% of patients may have an intermediate activity of the 6-MP/6-TGN detoxifying enzyme thiopurine methyltransferase due to genetic polymorphism. Reduced or absent TPMT-activity results in 2 to 3-fold or 10 to 20-fold higher 6-TGN tissue concentrations, thereby markedly increasing the likelihood of myelotoxic reactions to azathioprine, especially when the latter is combined with 5-amino salicylates, which themselves inhibit TPMT. However, the present patient had a high erythrocyte TPMT activity, and TPMT enzyme polymorphisms as well as toxic 6-TGN were absent. The latter findings suggest that azathioprine treatment was not the primary cause of exaggerated immunosuppression in the present case, since cumulative doses were low and duration of therapy was short. In addition, at least in Crohn's disease, leukopenia is, in most cases, not related to TPMT deficiency.

When leukopenia developed, immunosuppressive therapy was switched to cyclosporine and high doses of prednisolone, since severe bowel inflammation persisted. This highly active therapeutic regimen, which resembles treatment following solid organ transplantation, induced severe immunosuppression in a patient already suffering from leukopenia. From a retrospective point of view, early surgical intervention at this stage might have provided definite healing, thereby terminating the need for escalating immunosuppressive medication and in parallel markedly reducing the risk of opportunistic infections.

When the patient arrived at our hospital, immediate surgical intervention terminated intestinal inflammation, but subsequently severe infections ensued. Granulopoesis could be sufficiently stimulated by filgrastim treatment, but persistent lymphopenia, which probably resulted from high doses of prednisolone and cyclosporine, reflected severe deficiency of the adaptive immune system. While the diagnosis of invasive aspergillosis itself was predictive of a poor prognosis, the latter was markedly worsened by evolving disseminated VZV infection. Notably, it cannot be distinguished with certainty, whether disseminated herpes zoster resulted from primal infection or reactivation of VZV, with the latter being more probable since anti-VZV immunoglobulin G class was detected early in the course of disease. Notably, in contrast to typical varicella (chicken pox) exanthema, lesions in varying stages were not present at one time, but the exanthema presented homogenously. This finding may be suspective of haematogenous dissemination of VZV rather than generalized reactivation from multiple ganglia. In this context, to our knowledge, this is the first published case of intestinal VZV efflorescences (visible through the abdominal wall temporarily closed with a mesh) in a patient suffering from disseminated herpes

zoster. Whereas haematogenous dissemination may sufficiently explain intestinal VZV involvement, VZV latency in and reactivation from the celiac ganglion, as well as affection of afferent sympathetic fibers of the intestinal nerve plexus, have also been described. In bone marrow transplant recipients, the combination of abdominal symptoms and VZV skin efflorescences is associated with fatal outcome in 50% of cases despite appropriate antiviral therapy. The latter fact underlines the severity of illness in the present patient and calls for early detection and treatment in at-risk patients. Besides solid organ or bone marrow transplant recipients, patients with inflammatory bowel disease who are treated with highly active immunosuppressive regimes may represent such an at-risk population. Routine surveillance for reactivation of herpesviridae (i.e. herpes simplex, VZV and cytomegalovirus) may accelerate diagnosis and onset of life-saving antiviral treatment in these patients.

Ethical statement The data of the present case report have been obtained in a retrospective manner, and the respective patient has been treated according to standard treatment regimes of our hospital. All requirements for patient anonymity are in agreement with the recommendations for patient data publication of our hospital ethics commission. According to the latter facts, no ethics committee approval was necessary for publication of the present data. The patient's relatives consent to publication of the present manuscript.

Conflict of interest None.