Primary intestinal aspergillosis resulting in acute intestinal volvulus after autologous stem cell transplantation in a patient with relapsed non-Hodgkin lymphoma: report on a rare infectious complication and a review of the literature

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Primary intestinal aspergillosis resulting in acute intestinal volvulus after autologous stem cell transplantation in a patient with relapsed non-Hodgkin lymphoma: report on a rare infectious complication and a review of the literature

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ABSTRACT

Objectives: Since primary intestinal aspergillosis is a severe infectious complication with a high morbidity and mortality in immunocompromised patients, we want to draw attention to this rare entity and the importance of early recognition.

Methods: We report a case of documented primary intestinal aspergillosis in a patient receiving an autologous stem cell transplantation (SCT). Furthermore, this article gives a short reflection on the occurrence of invasive aspergillosis in autologous SCT and the value of serum galactomannan levels based on literature search and linked with the case.

Results: In this case the patient presented on day +8 after autologous SCT for a relapsed diffuse large B-cell lymphoma with an acute abdomen with urgent need for surgical intervention. Biopsy revealed the presence of fungal colonies due to aspergillosis and voriconazole was started. Until that day the systematically taken serum galactomannan tests were all negative or pending. Initially there was some resistance to perform surgery in the presence of neutropenia and thrombocytopenia but in the end it provided the definitive diagnosis and should not be delayed. Until now this patient is in good health and retains a complete remission.

Conclusion: With this case, we would like to emphasize that early recognition of primary intestinal aspergillosis is of the utmost importance as it is a rare but serious infectious complication. It should be included in the differential diagnosis of neutropenic patients with sudden onset abdominal pain and ongoing fever, even in the absence of a positive serum galactomannan.

KEYWORDS
Intestinal aspergillosis; serum galactomannan; stem cell transplantation; surgery

Case report

A 21-year-old man was admitted for an autologous stem cell transplantation (SCT) as consolidation therapy for relapsed diffuse large B-cell non-Hodgkin lymphoma of the nasopharyngeal cavity. Before the autologous transplant complete remission was obtained using salvage chemotherapy consisting of three cycles of rituximab (375 mg/m²), dexametasone (50 mg), high-dose ara-C (2 × 2000 mg/m²) and cisplatin (100 mg/m²) (R-DHAP). Peripheral autologous stem cells were collected after the second cycle of R-DHAP following granulocyte-macrophage colony-stimulating factor mobilization for 10 days. A high-resolution CT of the lungs and sinuses, performed as part of his pre-transplant workup, was normal (Figure 1(a)). The conditioning regimen was the standard BEAM-protocol (BiCNU/carmustine 300 mg/m², etoposide 200 mg/m² and cytarabine 200 mg/m² twice daily for 4 days and melphalan 140 mg/m²). No apparent complications were seen during conditioning and stem cell infusion but on day +3 the patient developed neutropenic fever for which broad-spectrum antibiotics (piperacilline/tazobactam 4 × 4g intravenous (IV)) were administered empirically. All cultures remained negative. White blood cell engraftment was reached on day +8 and was complicated by severe acute abdominal pain. CT imaging of the abdomen revealed obstruction of the small intestine (Figure 1(b)). The development of an acute abdominal syndrome with hemodynamic instability prompted an emergency laparotomy on day +8 showing volvulus involving the proximal jejunum with imminent perforation (Figure 1(c)). Repositioning and decompression was performed with creation of a temporary jejunostomy. Biopsies taken during the procedure revealed the diagnosis of an invasive mycosis, the branching of the hyphae was compatible with aspergillosis (anatomopathology, Figure 1(d) and e), but no fungal culture or PCR was performed. After starting IV voriconazole (6 mg/kg loading dose, followed by 4 mg/
kg maintenance) alongside conventional supportive therapy, infectious parameters decreased slowly. Galactomannan assays were systematically performed twice weekly during aplasia. The first positive sample was taken at day +7 (6,2), but was only known at day +11 and therefore after the surgical exploration. The definitive diagnosis of invasive aspergillosis was established by the combination of histopathology and a positive galactomannan test. After 7 days in the intensive care unit, the patient could be transferred back to the haematology ward. Persistent bleeding of the fragile intestinal mucosa was suspected due to a drop in haemoglobin and confirmed by CT angiography. Arterial embolization was performed at day + 21 and repeated at day + 34. Resection of the involved intestinal segment however, could be avoided.

A high-resolution CT of the lungs performed at day + 42 because of recurrent fever and coughing showed a lesion compatible with invasive pulmonary aspergillosis (Figure 1(f)), new compared to pre-transplant imaging (Figure 1(a)). As such, the diagnosis of a primary intestinal aspergillosis with secondary haematogenic spread to the lungs was assumed. Until this day there were no respiratory symptoms present.

Due to hepatotoxicity (total bilirubin 6.3 mg/dL, AST 112 U/L, ALT 99 U/L, yGT 887 U/L, alkaline phosphatase 482 U/L), voriconazole was temporarily switched to IV caspofungin (70 mg loading dose at the first day, followed by 50 mg once daily in maintenance). This was not related to toxic drug levels of voriconazole, ranging from 1.5 to 4.6 mg/L during treatment. After improvement of the liver enzymes, voriconazole could be

Figure 1. (a): Screening HRCT pre-SCT excluding pulmonary aspergillosis. (b): Contrast-enhanced CT abdomen showing marked dilatation of the small bowel alongside stranding of fatty tissues. (c): Surgical exploration showing volvulus of the proximal jejunum with imminent perforation. (d): Microscopy of the surgical specimen showing completely necrotic mucosa (Mu) and submucosa (SM) with numerous aspergillus hyphae. Haematoxylin and eosin staining, original magnification ×200. MM: muscularis mucosae. (e): High magnification showing acutely branching and septate aspergillus hyphae. Grocott’s methenamine silver staining, original magnification ×400. (f): Post-surgery HRCT showing presence of a multinodular lesion (tree-in-bud sign) with surrounding ground-glass infiltrates, suggestive of peri-lesional haemorrhage. As such, secondary pulmonary aspergillosis was suspected.
restarted at 250 mg twice daily per os. In total, this patient received antifungal therapy for 3 months, then therapy could be stopped considering the clinical, biochemical and radiographical resolution.

During the long period of revalidation that followed this severe complication, the patient suffered from cytomegalovirus reactivation for which consecutively gancyclovir and valgancyclovir were started. He also developed high fluid output of the jejunostomy, probably due to persistent inflammation of the intestinal lining. IV fluid replacement was needed alongside octreotide therapy. On day +99, a control colonoscopy showed the development of significant disuse colitis. As sufficient healing of the proximal jejunum was present, intestinal re-anastomosis was performed on day +102, completely alleviating high fluid output.

At his latest evaluation in February 2018 (more than 3 year after transplantation), the patient still remains in a complete remission and is in excellent general condition.

Discussion

The incidence of invasive aspergillosis in autologous SCT ranges from 2% to 6% (mean 4.8%) with a very high mortality (78−92%) [1]. The most recent published mortality rates in autologous SCT patients do however date from 15 years ago [1]. As mortality rates, associated with invasive aspergillosis, have declined over the past decade in haematology patients in general, prognosis in autologous SCT patients could also already be improved due to better supportive care and antifungal treatment [2,3]. Unfortunately, no up-to-date data concerning this patient population has been published recently. Invasive aspergillosis is most commonly seen in the respiratory tract and when present in the gastrointestinal tract, it is mostly in the context of disseminated disease. Besides inhalation, aspergillus spores can also be ingested, although primary intestinal aspergillosis is rare and the incidence is estimated around 1% of fungal infections. It may be underreported because of the difficult diagnosis which can sometimes only be made by autopsy, this presumptive underestimation is supported by the higher number of cases found in autopsy series [4,5].

Here, we described a case of primary gastrointestinal aspergillosis in which involvement of the lungs probably only developed afterwards, it was presented as an acute abdomen as early as day +9. In the literature we found a mean time to onset of 20 days after autologous SCT [1]. The incidence of primary gastrointestinal aspergillosis in the setting of autologous SCT cannot be found in literature, but few case reports were published [4,5]. Most of the reported patients with primary gastrointestinal aspergillosis have received an allogeneic SCT or high dose chemotherapy for acute myeloid leukaemia. In the setting of autologous SCT invasive aspergillosis in general and certainly primary gastrointestinal aspergillosis is much more rare, partly due to the shorter neutropenic period and a less immunocompromised state.

After ingestion, aspergillus spores cannot invade the intact mucosal barrier. In a SCT setting, however, like in the presented case, there are predisposing factors compromising the mucosal barrier such as neutropenia resulting in increased bacterial translocation or aggravating existing colitis, mucosal toxicity due to chemotherapy and use of steroids and/or broad spectrum antibiotics [2,6–9].

In contrast to the more commonly affected site of sino-pulmonary aspergillosis with clear symptoms and typical imaging, gastrointestinal disease is more difficult to detect and to prove. Radiological findings in gastrointestinal aspergillosis may vary from characteristic thickening of the bowel wall to an image of sub-obstruction with colon distension [10], as in this case, CT scan showed an obstruction of the small intestine. Furthermore a positive serum galactomannan assay in patients without evidence for respiratory involvement on CT scan is often considered as a false positive result. But some of them may be ‘true positive’ results localized at unusual sites of aspergillosis infection such as gastrointestinal and should prompt a more thorough search for aspergillus in other organs [11].

On the other hand, in a retrospective analysis by Kazan et al., galactomannan antigenaemia testing in proven gastrointestinal aspergillosis was only positive in 16 out of 25 patients (64%), including four of eight cases of isolated gut aspergillosis (50%). The frequency of performing the galactomannan assay was not mentioned [12]. A meta-analysis of Pfeiffer et al. found a sensitivity of 0.71 and a specificity of 0.89 for the galactomannan antigen test in general, when performed in haematological patients in specific they found a sensitivity of 0.70 and a higher specificity of 0.92. For those receiving a transplantation, the sensitivity was higher (0.82), but the specificity was lower (0.84) [13]. The serum galactomannan assay has a high specificity in neutropenic patients and the reproducibility is best in patients with a high pretest probability, so it should be used in this context [13,14]. In our centre, we only routinely perform serum galactomannan testing during the aplastic episode, as performed in the presented case. Two of the four cases of primary gastrointestinal aspergillosis with a false negative galactomannan test result in the retrospective analysis by Kazan were performed on non-neutropenic patients, which can explain the low sensitivity [12]. Marr et al. analysed the galactomannan assay in patients with proven aspergillosis and they could not find a positive test result in those without neutropenia; on the contrary 80% of the neutropenic patients did
have a positive galactomannan. They suggested that non-neutropenic patients develop less extrapulmonary dissemination resulting in a reduced sensitivity [15].

In several series of case reports, gastrointestinal involvement required tissue preservation by surgery to confirm the diagnosis due to aspecific symptoms, imaging findings and negative serum galactomannan [6,12]. However, surgery of neutropenic patients is generally avoided whenever possible, leading to underdiagnosis of gastrointestinal aspergillosis. Our patient presented with an acute abdomen without any respiratory symptoms or other evidence of a primary respiratory localization, requiring urgent laparoscopic intervention. The result of the serum galactomannan, performed biweekly as part of the standard monitoring during the neutropenic period, was not readily available when the decision to perform surgery was made and only came back positive after acute branching aspergillus hyphae were seen on the surgical biopsy specimen. The finding that the lesion was transmucosal can attribute to the argument that the aspergillosis was primary gastrointestinal.

There are no clear recommendations for the management of gastrointestinal aspergillosis available. A successful two-step approach in surgery – with first resection and decompression with construction of a stoma and re-anastomosis after recovery – is described in case reports [16]. Commonly, a combination of medical and surgical treatment is needed [12]. Surgery makes an opportunity to reduce fungal burden and to resolve complications as the obstruction in our presented case [12]. Prolonged exposure to specific antifungals is advised for the treatment of documented infections, with a minimum of 6–12 weeks. Although exact duration of therapy is not well defined, it need to be continued until clinical, antigenemic and radiographic normalization and as long as the patient remains under immunosuppression [17].

Primary intestinal aspergillosis is generally associated with a very poor prognosis and results in a high risk for disseminated disease, partly due to late diagnosis. In a case series, 53% of the haematological patients survived at 3 months. Patients who underwent surgery had a slightly higher chance of survival (41.7%) compared to those who did not (33.3%) [12]. Our patient urgently underwent a laparotomy with the construction of a temporary jejunostomy, in addition he received antifungal therapy for 3 months and until this day he remains in good health and in complete remission.

Conclusion

Intestinal aspergillus is rare and associated with high mortality. It should therefore be included in the differential diagnosis of neutropenic patients with sudden onset abdominal pain and ongoing fever, certainly when a positive galactomannan is seen in the absence of sino-pulmonary symptoms/lesions. Also, our case illustrates that a pending serum galactomannan test result, even in the presence of prior negative results, should not delay surgical exploration as an acute primary intestinal aspergillosis cannot be ruled out.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References


