Potential role of tocilizumab in severe gastrointestinal barrier damage after car t-cell therapy

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Potential Role of Tocilizumab in Severe Gastrointestinal Barrier Damage after CAR T-Cell Therapy

Short title: Tocilizumab after CAR T-cell Therapy

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Abstract

We report a septicemia and disseminated candidiasis due to delayed gastrointestinal mucosae repair in a patient treated with tocilizumab after anti-CD19 CAR T-cell therapy. Tocilizumab could have inhibited intestinal tissue repair and furthered bacteria translocation leading to the invasion of intestinal mucosa by yeasts as IL-6 is known to be involved in mucosal wound healing.

Short communication

Introduction

Adoptive transfer of chimeric antigen receptor T-cells (CAR T-cell) targeting CD19 has emerged as one of the most promising approaches for treating patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).[1,2] Accordingly, the two approved anti-CD19 CAR T-cell products, tisagenlecleucel (CTL019, Kymriah™) and axicabtagene ciloleucel (axi-cel, Yescarta™) have demonstrated durable remission in approximately 30-40% of patients with DLBCL. Yet, this approach can be responsible for severe adverse events, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[3] Therefore, close patient monitoring is a critical part of the treatment protocol for the first two weeks after CAR T-cell infusion. High-grade CRS and ICANS are managed with the use of immunosuppressive agents such as tocilizumab (anti-IL6 receptor) and corticosteroids.[4] In addition, prior therapies and lymphodepleting conditioning coupled with the use of tocilizumab and corticosteroids can increase patient infection risk.[5] We report the first case of a heavily pretreated patient developing severe gastrointestinal (GI) damage leading to unexpected septicemia and further disseminated candidiasis following CAR T-cell therapy. The issue of potential role of tocilizumab in the delayed GI wall repair has been addressed.

Case report

A 68-year-old female received CAR T-cells (axi-cel) for heavily pretreated (5 prior lines of therapy) DLBCL evolved from follicular lymphoma. After leukapheresis, a bridging therapy consisting of 2 cycles of DHAP (dexamethasone, high dose aracytine, cisplatin) was given allowing disease stability. Lymphodepleting conditioning (cyclophosphamide 500 mg/m²/day and fludarabine 30 mg/m²/day for 3 days) was initiated. However, the axi-cel infusion at (2×10^6 CAR T-cells per kilogram) was delayed and ultimately given 5 days after the end of lymphodepletion (41 days after leukapheresis) due to sudden cauda equina syndrome development related to lymphoma progression with epiduritis. Salvage treatment with dexamethasone 40 mg/day for 4 days and radiotherapy for 5 days were therefore required.

Grade 1 CRS occurred on day 1 after infusion of axi-cel, evolving in grade 2 on day 4 with hypoxemia requiring a single dose of tocilizumab. Grade 3 ICANS occurred on day 6 after axi-cel without fever recurrence requiring 10 mg IV dexamethasone four times a day according to European Society for Blood and Marrow Transplantation recommendations.[4] On day 8, ICANS resolved and the patient started neutrophil recovery. Dexamethasone was progressively tapered and discontinued on day 13. On day 14 after axi-cel, the patient developed sudden abdominal pain and diarrhea associated with hypotension and cardiac arrest without fever. Despite intensive care management, a second cardiac arrest occurred and was resolved with adrenaline. Meropenem-sensitive *Escherichia coli* was isolated from peripheral blood cultures. A computerized tomography-scan showed, without clear defect, a thickening of the large intestine walls and almost all the small loops. A laparotomy ruled out mesenteric ischemia. Microbiological examination of peritoneal fluid was sterile. High dose noradrenalin remained necessary and inflammation markers persist (CRP 150 mg/L) contrasting with progressive procalcitonin decrease. On day 20 after axi-cel, high serum levels β-(1,3)-D-glucan (1547 pg/ml) and mannan (>2500pg/ml) raised suspicion of invasive Candida

infection. Serum galactomannan was positive (index >6) which contrasted with negative DNAemia for *A. fumigatus*. The patient died on day 21 and autopsy was performed.

Postmortem analysis

Postmortem analysis macroscopic findings showed diffuse petechiae (lungs, pleura, spleen, liver, heart, omentum, colon, kidney) indicating hypoxia. The sectioning of lungs revealed a thick and viscous brown mucoid bronchial secretion. The peritoneal cavity contained 2-liter hemoperitoneum. In the upper GI tract—from lips to the Treitz ligament—a duodenal ulcer without perforation (3.2 x 2 cm) was found (Figure 1A). In the lower GI tract—from the Treitz ligament to anus—there were no signs of ischemia but presence of pseudomembranous plaques on bowel serosa. No suspect lymph nodes were found. In microscopic examination, the duodenal ulcer was confirmed with total loss of mucosae reaching the musculosa. The mucosae were replaced by yeasts, pseudohyphae and hyphae. Moreover, stomach walls, from mucosa to serosa, and the rest of the bowels had also been invaded by fungal cells (Figure 1B). The pseudomembranes contained numerous fungi. Periodic-acid Schiff and Grocott stains confirmed the presence of mycelial agents (Figure 1C). mycotic emboli were also found in the liver and lungs (Figure 1D and 1E). All lymph nodes were lymphoma-free.

Microbiological examination of postmortem samples

Direct microscopic examination of the gut epithelium barrier and bronchial mucus revealed numerous yeasts associated with pseudomycelia and Candida albicans grew in culture on Sabouraud agar and chromogenic media. Abdominal effusion fluid examination revealed rare colonies of *C. albicans*. One colony of *Aspergillus fumigatus* grew in bronchial mucus and abdominal fluid cultures but not in the gut epithelium barrier. These mycological findings were associated with the presence of oropharyngeal polymicrobial flora in the two gut samples. Mucorales and *A. fumigatus* q-PCR were negative on all postmortem samples.

Galactomannan (index > 6) and mannan (>2500 pg/mL) measurements in the abdominal effusion fluid were also positive.

Discussion

Besides CRS and ICANS, which are early complications in most patients undergoing CAR T-cell therapy, infectious complications in this setting are frequent but often less severe. Neutropenia following lymphodepleting conditioning is a commonly reported risk factor of early infectious complications, mainly bacterial infections, affecting 23% of patients. Conversely B-cell aplasia is a risk factor of late infectious disease events, mainly viral infections, affecting 9% of patients. Recently, 32 days after CAR T-cell infusion, a patient receiving tocilizumab and high dose corticosteroids developed fatal mycobacterium abscesses.[6] The use of tocilizumab and corticosteroids for lower grades of CRS and ICANS could increase the incidence of early infection. Hill *et al.* reported 3% of invasive fungal infection (IFI) in patients receiving anti-CD19 CAR T-cell therapy; all patients had severe CRS or ICANS requiring tocilizumab and/or corticosteroids.[5] While corticosteroids are a risk factor for invasive hyphae infection such as aspergillosis, their role in invasive candidiasis is controversial.[7] Invasive fungal infection could have been sped up by septic shock and aminoglycoside use. This hypothesis is supported by the timing of the invasive candidiasis not found by the laparotomy conducted on D+14.

Although rare after CAR T-cell therapy, radiation- and chemotherapy-induced GI mucositis is a frequent complication in patients with hematological malignancies. GI mucosa repair is observed within two weeks after the end of cytotoxic treatment and usually concomitant to neutrophil recovery. In the current case, a loss of the entire GI mucosae was noted in the postmortem analysis. Severe GI barrier damage due to the use of prior therapies including abdominal irradiation and the further administration of tocilizumab could have promoted

Escherichia coli translocation and further septicemia. Indeed, prior cytotoxic therapies may have been responsible for GI barrier damage while, in parallel, tocilizumab, a monoclonal antibody against human interleukin-6 (IL-6) receptor, may have contributed to delayed GI wall repair and GI mucosae recovery. As apart from its role in inflammatory response, IL-6 is also known to be involved in mucosal wound healing.[8] Furthermore, tocilizumab is known to cause adverse GI events such as ulcers in the small and large intestine and intestinal perforation among rheumatoid arthritis patients who have received tocilizumab therapy in clinical trials.[9] Tocilizumab could have inhibited intestinal tissue repair and furthered bacteria translocation leading to the invasion of intestinal mucosa by yeasts. Since invasive fungal infections are uncommon in CAR T-cell recipients, there is no evidence suggesting the use of systematic anti-fungal prophylaxis, but it should be considered for patients with prolonged neutropenia who are on corticosteroids.[4,10] In addition, the use of proton pump inhibitor is to be considered in patients undergoing CAR T-cell therapy, especially when corticosteroids and tocilizumab are administered.

To our knowledge, this is the first report of septicemia and disseminated candidiasis due to delayed GI mucosae repair in a patient treated with anti-CD19 CAR T-cell therapy and tocilizumab. Given its potential GI toxicity, close monitoring of GI events in patients receiving tocilizumab following CAR T-cell therapy is recommended. Furthermore, tocilizumab should be used with precaution in patients having recently received abdominal irradiation or who present other conditions that might alter the GI wall.

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Competing Interests

The authors have no conflicts of interest to declare.

Authors' contribution

IYA, BS and FM conceived the study; OK, SL, RN and ML acquired data; DB, OK, SM and ASM analyzed data; DB, OK, SL and BS wrote the original draft; all authors revised and approved the final manuscript

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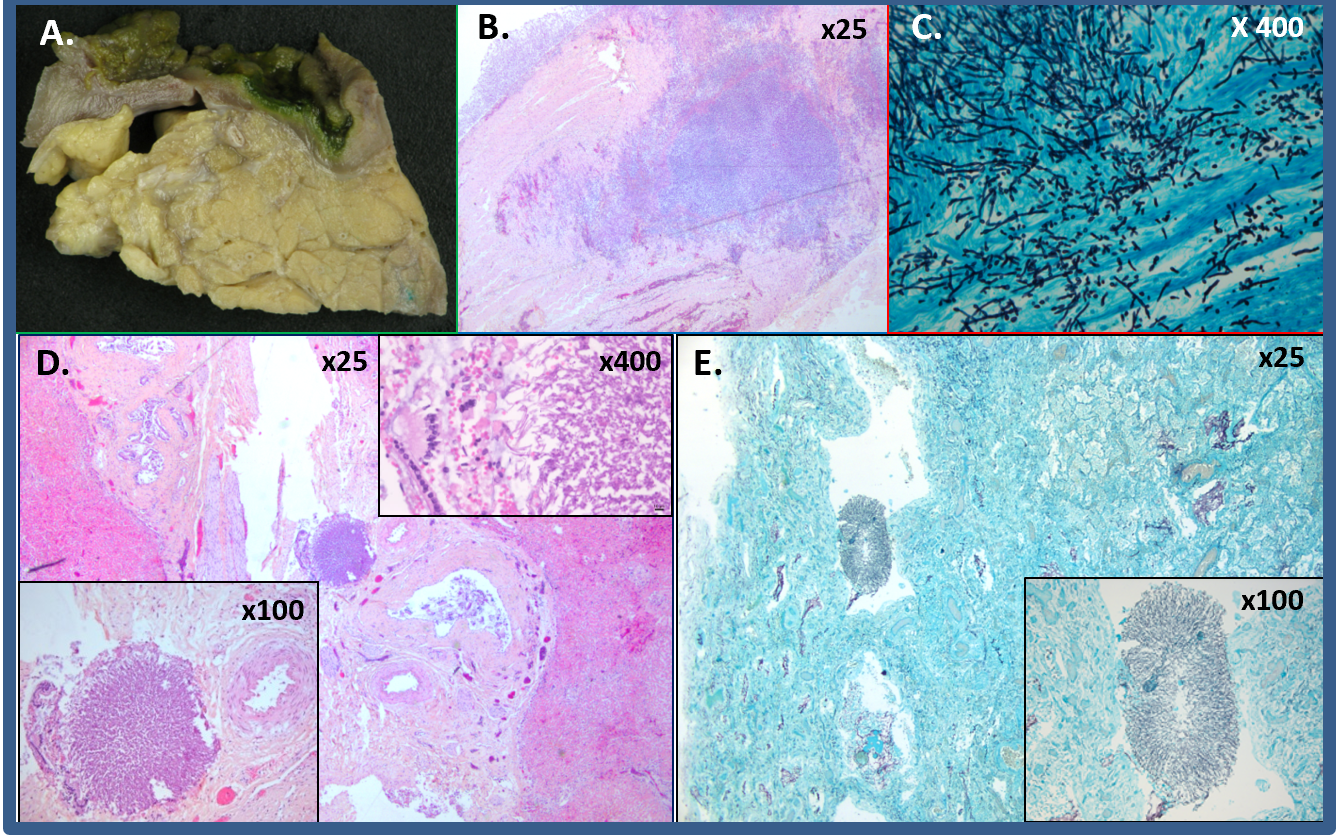
Figure legend

Figure 1. Autopsy showing several digestive lesions including: **(A)** duodenal ulcer (macroscopic view), while histological examination of duodenal walls revealed the absence of the gut epithelium barrier associated with tissue invasion by yeasts, pseudohyphae and hyphae (**B:** hematoxylin-eosin (HES) x25, **C:** Grocott x400). Tissue invasion by fungi was also observed in hepatic (**D:** HES x25, x100 and x400) and pulmonary (**E:** Grocott x25 and x100) intravascular emboli.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