Olecranon bursitis caused by *Scedosporium apiospermum* in a patient treated with CAR-T cells

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ABSTRACT

Chimeric antigen receptor (CAR-) T cell therapy is a relatively new form of immunotherapy for hematological malignancies. Although patients are at increased risk of infection following CAR-T cell therapy, reports of fungal infections are scarce. We report a case of *Scedosporium apiospermum* infection causing bursitis of the elbow in a lymphoma patient after treatment with CAR-T cells. The fungal bursitis relapsed under posaconazole treatment, but was cured after surgical extirpation of the bursa.

1. Introduction

*Scedosporium* species are filamentous fungi that are found everywhere in the environment, including in soil and polluted water. They can cause infections in immunocompromised hosts, but also in immunocompetent hosts, and are difficult to treat due to their intrinsic resistance against multiple antifungal agents [1,2]. Infections in immunocompetent hosts tend to be localized, for example to the eye, soft tissue or bone after trauma, or the lung or central nervous system after near-drowning accidents. Disseminated disease is much more common in immunocompromised patients and is associated with high mortality rates, especially after hematopoietic stem cell or solid organ transplantation (68% and 57% mortality, respectively) [3,4].

Recently, a new form of immunotherapy was introduced to treat patients with hematological malignancies; chimeric antigen receptor T cell (CAR-T) cell therapy, in which T cells from a patient are re-engineered in vitro so that they recognize and bind to specific antigens on the surface of cancer cells [5]. Patients treated with CAR-T cell therapy are at increased risk of infection due to pre-treatment with chemotherapy and the specific effects of CAR-T cells on normal B cells and antibody production, and invasive fungal disease has been reported both early and late after CAR-T cell therapy [6]. Here we present a patient treated with CAR-T cell therapy who developed a bursitis of the olecranon caused by *Scedosporium apiospermum*.

2. Case presentation

A 44-year old patient presented in November 2020 with a bursitis of his left elbow (day 0). Six months earlier (day – 202) he was treated with lymphodepleting chemotherapy directly followed by CD19-specific CAR-T cell therapy for recurrence of follicular lymphoma. He was considered immunocompromised, with total neutrophils and lymphocytes slightly below normal levels, absent B-cells, and a treatment associated persistent hypogammaglobulinaemia. Four weeks before presentation at our hospital he had contacted his general practitioner (GP) because of swelling and pain of his left elbow. His GP had aspirated fluid from the elbow, injected steroids and started antibiotics, but now there was recurrence of swelling and pain. Bursitis without arthritis was diagnosed by a rheumatologist and the bursa was surgically opened and drained, relieving pus.

The patient was started on oral flucoxacinill (500 mg, four times daily) and sent home. On day +2 the culture of the pus from the bursa grew white colonies on a Sabouraud dextrose agar plate, showing long conidophores with large oval conidia on microscopy (Fig. 1).

*Scedosporium* infection was suspected, and the patient was switched to voriconazole therapy (200 mg, twice daily, orally). A PET-CT scan did not show signs of systemic involvement and blood cultures remained negative. Because of vivid hallucinations and sleeplessness persisting for four days after starting voriconazole (day +6) the patient was switched to posaconazole 300 mg a day and drug plasma concentrations were monitored. Over the next few weeks the bursitis symptoms decreased.
The fungal isolate was identified as *S. apiospermum* using beta-tubulin sequence analysis and MICs were determined using the EUCAST reference method (voriconazole 0.5 mg/L, posaconazole 1.0 mg/L). Voriconazole is considered first line treatment for *Scedosporium* infections [2]. However, posaconazole was continued because of the side effects experienced by the patient on voriconazole and the lack of alternative treatment options for *Scedosporium* infections. At day +65 after his initial presentation, swelling of the patients’ elbow returned and an ultrasound again showed a significant bursitis. Fluid was aspirated and cultures again grew *S. apiospermum* even though the patient was still using posaconazole with adequate drug concentrations (>1.5 mg/L). Susceptibility testing was repeated and showed a posaconazole MIC of 2.0 mg/L and a voriconazole MIC 1.0 mg/L and to prevent systemic spread of the infection the bursa was surgically extirpated; direct microscopy (Blankophor® staining) showed fungal hyphae. Eight weeks later (day +119) there were no signs of bursitis and posaconazole was discontinued.

3. Discussion

CAR-T cell treatment is a relatively new form of immunotherapy and can render patients immunocompromised for months or longer after treatment. The CD19-specific CAR-T cells that the patient received have “on-target, off-tumor” effects because the target antigen CD19, a transmembrane glycoprotein, is expressed on malignant as well as normal B-cells, resulting in B-cell aplasia and hypogammaglobulinaemia that can persist for months or even years [7,8].

Fungal infections reported following CAR-T cell treatment include infections with *Candida*, *Aspergillus*, *Fusarium*, *Pneumocystis jirovecii* and Mucorales [9–13], but so far the consensus in the literature is that (invasive) fungal infections after CAR-T cell treatment are uncommon, at least compared to bacterial and viral infections [13–15].

Here we report the first case of a *Scedosporium* infection in a patient treated with CAR-T cells. Fortunately, even though the patient was immunocompromised, and could not continue first-line treatment with voriconazole because of side effects, he did not develop a disseminated infection and was cured with a combination of posaconazole treatment and surgical resection. Pharmacological treatment options for *Scedosporium* infections are limited due to their intrinsic resistance to various antifungal agents, including amphoterin B, and the European guidelines emphasize the importance of surgical debridement for localized infections, especially in immunocompromised patients [2]. Two new broad-spectrum antifungals with different mechanisms of action, olorofim and fosmanogepix, showed promising activity against *Scedosporium* in (industry sponsored) in-vitro and mouse studies [16–18]. Interestingly, CAR-T cell therapy targeting the β-glucan component of the fungal cell wall has also been proposed as a potential treatment for *Scedosporium* and other invasive fungal infections [19].

In conclusion, although the current literature suggests that invasive fungal infections are rare following CAR-T cell therapy, physicians should remain alert for opportunistic infections, such as infections with *Scedosporium* species, since these can be difficult to treat, may require surgery and prolonged antifungal therapy, with limited antifungal options.

Declaration of competing interest

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Ethical statement

Written informed consent was obtained from the patient.

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Fig. 1. Cotton blue staining from fungal colony growing on a Sabouraud dextrose agar plate (200x). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
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