

A case report of locally invasive *Aspergillus fumigatus* infection in a patient on canakinumab

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Received 31 May 2018; accepted 17 August 2018; online publish-ahead-of-print 4 September 2018

Background

Canakinumab is a human monoclonal interleukin-1 antibody that has been studied in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial and shown to prevent recurrent cardiovascular events, while increasing the incidence of neutropenia and risk of severe infections.

Case summary

This is a case report of a locally invasive aspergillus infection in a patient with uncontrolled diabetes mellitus who was receiving canakinumab for 3.5 years as part of the CANTOS trial. He presented with headaches and left eye pain and was found to have a large left ethmoid sinus mass extending into the orbit on computed tomography scan of the head. Cultures from an endoscopic biopsy of left ethmoid sinus grew *Aspergillus fumigatus*. Canakinumab was discontinued, and he was discharged on voriconazole with improvement in his headaches and left eye pain.

Discussion

The anti-inflammatory properties of canakinumab could have blunted the patient's immune response allowing the mycetoma to invade adjacent tissue. If canakinumab was approved for the secondary prevention of cardiovascular events then it is important to be cognizant of its potential to delay the presentation of any infection.

Keywords

Case report • *Aspergillus* • Canakinumab • CANTOS • Mycetoma • Ethmoidectomy

Learning points

- Canakinumab may alter and delay the presentation of infection.
- It is very important to educate patients about alerting providers of any new symptoms and thoroughly screen for infections, including locally invasive fungal infection.

Introduction

Canakinumab is a human monoclonal IL-1 β antibody and targets IL-1 β dependent inflammation. It is approved for the treatment of cryopyrin-associated periodic syndromes in 2009 by both the Food and Drug Administration and the European Medicines Agency.¹

Canakinumab induced inhibition of inflammation could potentially preserve pancreatic beta cell function and decrease the progression of atherosclerosis in coronary arteries of patients with Type 2 diabetes mellitus (DMII) who are at significantly higher risk of developing coronary artery disease. Interleukin-1 β inhibition with canakinumab markedly reduces plasma levels of interleukin-6 and high-sensitivity

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C-reactive protein (hsCRP). Canakinumab is being studied in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS), a double-blinded randomized control trial, to determine whether the long-term inhibitory effects of canakinumab on inflammation decreases the rate of cardiovascular events in patients who are at an increased risk due to elevated levels of hsCRP.² Here, we report a case of locally invasive aspergillus infection in a patient who was receiving canakinumab for 3.5 years as part of the CANTOS trial.

Timeline

Day 0	Presentation with left eye pain and headaches in a patient who has been on canakinumab for 3.5 years. Computed tomography head revealed soft tissue density mass in the left ethmoid sinus with erosion of the medial orbital wall, left cribriform plate, and anterior cranial fossa. Patient was admitted for surgery.
Day 1	Endoscopic left total ethmoidectomy with biopsy of left ethmoid and orbital mass was performed and preliminary pathology was significant for mycetoma. Infectious disease was consulted. He was started on intravenous imipenem (to cover potential <i>Actinomyces</i> and <i>Nocardia</i>) and liposomal amphotericin infusion. Canakinumab was discontinued.
Day 2	Amphotericin dosing was increased. Ophthalmology evaluation did not reveal any optic nerve compression.
Day 5	Developed acute kidney injury from the amphotericin. Fungal pathology was suggestive of mould.
Day 6	<i>Aspergillus fumigatus</i> was isolated on culture. Antibiotics switched to voriconazole. Headache, swelling, and vision were improving.
Day 9	Discharged home on voriconazole. Headaches and acute kidney injury improved.

Case summary

The patient is a 63-year-old man with a history of acute myocardial infarction, coronary artery bypass surgery with stent implant prior to enrolment in the CANTOS trial, systolic heart failure with left ventricular ejection fraction of 40%, implant of cardioverter defibrillator, DMII (on home insulin glargine 32 units daily), chronic kidney disease Stage III (baseline creatinine 1.4 mg/dL), and a recent history of left 2nd toe amputation for a diabetic foot infection who had been on canakinumab 300 mg every 3 months as a CANTOS trial participant for 3.5 years. He does not have a history of recurrent sinusitis or other systemic infections. His social history was relevant for frequent gardening. He presented with a 1 week history of headaches and blurry vision.

On examination, he was afebrile and haemodynamically stable with left ptosis and left periorbital tenderness, with an otherwise



Figure 1 A computed tomography head upon presentation significant for a soft tissue density mass in left ethmoid sinus with erosion and extension into the orbital space.

normal neurological examination. Initial ophthalmologic examination revealed decreased visual acuity on the left eye (20/70), pupils were equal round and reactive to light bilaterally with intact extraocular muscle movement. His left eye had decreased temporal and superior nasal field deficits and his right eye had superior nasal field deficits. Left eye dilated eye examination was significant for a large cup to disc ratio, attenuated vasculature with scattered micro-haemorrhages and a small intra-retinal haemorrhage supero-nasal to the optic disc. His left 2nd toe amputation site showed good healing. Laboratory evaluation was significant for haemoglobin A1C of 8.2% with recent values as high as 10.5%, white blood cell (WBC) count 4400/mL (normal 3700–9700/mL) with 55.0% neutrophils and creatinine 1.26 mg/dL (0.60–1.20 mg/dL). Erythrocyte sedimentation rate (ESR) was 38 mm/h (normal 0–15 mm/h), and C-reactive protein (CRP) level was 0.9 mg/dL (0.0–0.5 mg/dL). Computed tomography (CT) head with contrast was notable for a soft tissue mass in left ethmoid sinus extending into orbit with erosion of anterior cranial fossa (Figure 1). Nasal endoscopy revealed a mass in the left posterior ethmoid cell with material consistent with mycetoma and non-necrotic surrounding mucosa. Debridement with left ethmoidectomy was performed. Fungal culture from his left posterior ethmoid biopsy grew *Aspergillus fumigatus*. There was no evidence of angioinvasion on pathology. No ophthalmologic involvement was present on serial eye exams.

He was initially started on 1000 mg every 6 h of intravenous imipenem–cilastatin and 800 mg daily of liposomal amphotericin but developed acute kidney injury while on amphotericin. Once culture data became available, he was transitioned to oral 300 mg every 12 h of voriconazole. Canakinumab treatment was discontinued. He was

discharged after resolution of acute kidney injury and improvement in his symptoms with a plan to complete several months of therapy for possible mycetoma-associated osteomyelitis. He was discharged on an increased dose of glargine of 35 units daily and glipizide 5 mg daily for better glycemic control.

He continued voriconazole and laboratory testing confirmed adequacy of his dosing regimen of 300 mg every 12 h (voriconazole trough level was 1.6 µg/mL). The patient continued to do well on outpatient voriconazole therapy for 3 months before developing right sided headaches. He reported no fevers or chills and laboratory evaluation did not show leucocytosis (WBC count was 3400/mL with 55.4% neutrophils). Haemoglobin A1C was 7.0%, ESR 37 mm/h, and CRP was 1.2 mg/dL. Repeat CT imaging of his head without contrast revealed improved disease at the site of prior aspergillus infection in the left ethmoid air cells but increasing density and debris in his maxillary sinuses bilaterally (Figure 2). He underwent endoscopic debridement of his maxillary sinuses and was found to have pathology consistent with mycetoma from his right maxillary sinus without evidence of tissue invasion; his fungal cultures did not reveal any growth at 1 month. Voriconazole was subsequently discontinued. Repeat CT imaging of his head 6 months later showed interval resolution of the inflammatory changes involving the left ethmoid air cells and the medial aspect of the left orbit and no evidence of the recurrent acute sinusitis. There was mild mucosal thickening of the residual ethmoid cells and bilateral maxillary sinuses. Patient has been off of the CANTOS study since the sinus infection and was asymptomatic in his 8 month post-discharge hospital follow-up.

Discussion

Patients develop invasive systemic or pulmonary aspergillosis, primarily from inhalation. Risk factors for developing this include prolonged or severe neutropenia, poorly controlled diabetes mellitus or an immunocompromised state.³ Gardening potentially exposed this patient to *A. fumigatus*. The lack of classic signs and symptoms of infection, despite the increasing size of his presenting mass, is unusual and potentially related to canakinumab therapy. We postulate that the anti-inflammatory properties of canakinumab were blunting this patient's immune response thus allowing his mycetoma to invade adjacent tissue. Although no evidence of angioinvasion was determined pathologically, his initial imaging was highly concerning for concomitant osteomyelitis, and he received an extended course of voriconazole therapy. Infection is the most common adverse effect reported with the use of canakinumab; however, there was no significant difference in the incidence of opportunistic infections between the groups that received canakinumab and placebo.² In a multicentre nationwide study from France involving both adults and children receiving canakinumab for various rheumatologic conditions, 13% of patients had mild respiratory infections, 9% had liver toxicity, and 4% had injection site reactions.⁴

The incidence of zygomycosis is higher in patients with DMII. A French population based study examining the trends in the incidence of zygomycosis between 1997 and 2006 reported a 9% per year increase in the incidence of zygomycosis in patients with DMII.⁵ Interestingly, a pooled analysis of the safety and tolerability of canakinumab in DMII patients from three randomized double blind trials



Figure 2 Repeat computed tomography imaging 3 months after initial presentation showing improved infection in left ethmoid sinus air cells and left orbit but an increased mucosal disease in the maxillary sinuses bilaterally with new high-density contents.

concluded that there was a small, non-significant increase in the incidence of infection in canakinumab users compared with those receiving placebo.⁶ However, the incidence of delayed fungal infections in patients who had been exposed to canakinumab therapy has not been reported.

Conclusions

If canakinumab was approved for the secondary prevention of cardiovascular events, it is likely to be prescribed to a large number of patients with diabetes. Therefore, it is crucial to be cognizant of how canakinumab therapy may alter and delay the presentation of infection in order to educate patients about alerting providers of any new symptoms and thoroughly screen for infections, including locally invasive fungal infection.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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