ABSTRACT
Advanced age and associated comorbidities are recognized predictors of life-threatening adverse outcomes, such as opportunistic infection following immunosuppressive therapy. We describe the case of an elderly patient with strictureing colonic Crohn’s disease and significant clinical comorbidities, initially controlled with corticosteroid induction followed by infliximab, whose course was complicated by fatal disseminated cryptococcal infection and posterior reversible encephalopathy syndrome. Our patient’s case highlights rare, but serious, complications of immunosuppression. In applying modern treatment paradigms to the elderly, the clinician must consider the potential for more pronounced adverse effects in this potentially vulnerable group, maximizing benefit and minimizing harm.

INTRODUCTION
The incidence of opportunistic infections in inflammatory bowel disease (IBD) patients on biological therapies such as infliximab is low (0.2%–1.1%). However, advanced age at initiation and comorbidities may be associated with serious adverse outcomes, including life-threatening infections and death. The rising global prevalence of older patients with IBD, considerations around advancing age and associated comorbidity, and the potential for more pronounced adverse effects pose a myriad of challenges to the clinician, further limited by the paucity of clinical data and consensus guidance in making evidence-based therapeutic decisions. Meanwhile, posterior reversible encephalopathy syndrome (PRES), a rare clinico-radiological entity characterized by headache, altered mental functioning, seizures, visual disturbance, and pathognomonic vasogenic oedema on magnetic resonance brain imaging, has been associated with infliximab in several published reports in the IBD literature.

CASE REPORT
A 74-year-old woman underwent a screening colonoscopy following a positive fecal occult blood test. Her medical history included type 2 diabetes mellitus, hypertension, ischemic heart disease with myocardial infarction, prior coronary artery bypass graft, and coronary stents. Colonoscopy revealed patchy inflammatory changes and a 2-cm ulcerated impassable stricture at the hepatic flexure with an impression of skip ulcerations (Figure 1). Histology confirmed erosive inflammatory changes at the hepatic flexure stricture and focal patchy ulcerations in the transverse colon. Upon direct questioning, she gave a history of right lower abdominal pain over a few months, without obstructive symptoms. Computed tomographic colonography confirmed the clinical impression of colonic Crohn’s disease (Figure 1). She later developed rectal bleeding. After comprehensive discussion of treatment options...
(including surgery), the patient opted in favour of a trial of medical therapy. An induction course of 40-mg prednisolone was prescribed, and in preparation for infliximab, prophylactic vaccinations were administered. She had an excellent clinical response to standard infliximab induction with complete symptom resolution and stricture healing confirmed on subsequent magnetic resonance imaging.

She was readmitted a day prior to her first 8-weekly maintenance infliximab infusion, with headaches, confusion, fever, rigors, and generalized body aches. She was on prednisolone at 20 mg daily at the time, with instruction to taper by 5 mg per week. On examination, she was pyrexial (38.3°C), tachycardic (120/min), tachypnoeic (32/min), and hypertensive (208/80 mm Hg). Infliximab was withheld and screening investigations for infection, including blood and urine cultures, chest and abdominal radiographs, and computed tomographic brain imaging were performed; her radiological investigations were normal. Her c-reactive protein was elevated (186 mg/L) and inflammatory markers necessitating another increase, becoming increasingly unwell.

Interim blood cultures returned positive for Cryptococcus neoformans and intravenous antifungal therapies; liposomal amphotericin (Ambisome) and flucytosine were commenced. Her hypertension proved refractory to incremental beta-blockers and calcium channel blockers, with options limited by significant renal impairment (glomerular filtration rate 18 mL/min). Subsequently, she had 2 seizures and cerebral magnetic resonance imaging confirmed a diagnosis of PRES (Figure 2) requiring intravenous labetalol, glyceryl trinitrate, and phenytoin infusions. Serum cryptococcal antigen levels were high (1:1024), raising clinical suspicion of disseminated Cryptococcus. Lumbar puncture confirmed cryptococcal meningitis with positive India ink stain and cerebrospinal fluid culture for Cryptococcus neoformans and cryptococcal antigen positivity at 1:256. Further antifungal therapies were guided by cerebrospinal fluid culture results and the specialist input of the regional infectious diseases unit. After 8 weeks, the patient was discharged from hospital on consolidation oral antifungal therapy (voriconazole) and close follow-up. At follow-up, a week later, she was in steroid-free IBD clinical remission without needing further infliximab but had signs of infection with high inflammatory markers necessitating another hospitalization. She was treated for sepsis, ongoing cryptococcal infection, and renal failure. Her condition deteriorated despite appropriate supportive therapy, and she died 2 weeks later.

DISCUSSION

This case highlights the potential for more pronounced adverse effects from immunosuppression in an elderly patient with IBD and comorbidities with several important learning points.

Our patient had received bimodal immunosuppression with antitumor necrosis factor alpha (TNFα) and corticosteroids. While the risks of anti-TNFα are widely appreciated, corticosteroids (eg, prednisolone 20 mg daily or more) also constitute meaningful immunosuppression with a higher risk of opportunistic infection and mortality. Indeed, recent studies demonstrate a lower uptake of anti-TNFα therapies in elderly IBD but a disappointingly lower threshold to use corticosteroids, possibly driven by physician misperception of risk. Corticosteroids should be used in an appropriated manner in both dose and duration with clear contingency planning.

Cryptococcosis is a rare opportunistic infection, with several previous cases in the IBD-specific anti-TNFα literature and 28 cases in the wider anti-TNFα literature. It is usually acquired by inhalation of an encapsulated yeast (from bird droppings) and is usually only clinically significant in the immunocompromised patient. Central nervous system infection, as in our
and immunosuppression.\textsuperscript{14} While the exact pathophysiological mechanism of PRES remains controversial, immunosuppressive drugs such as infliximab may be implicated by causing endothelial injury to the blood-brain barrier, leading to a sequence of vasocnstriction, hypoperfusion, and extravasation of fluid.\textsuperscript{15}

Another intriguing complication in our case was PRES, where corticosteroids are also likely to have been a contributory factor to the severe, refractory hypertension (seen in 75\% of cases), alongside other predisposing factors, including severe infection and immunosuppression.\textsuperscript{14} While the exact pathophysiological mechanism of PRES remains controversial, immunosuppressive drugs such as infliximab may be implicated by causing endothelial injury to the blood-brain barrier, leading to a sequence of vasocnstriction, hypoperfusion, and extravasation of fluid.\textsuperscript{15}

In applying modern treatment paradigms to elderly patients with IBD, clinicians must consider the potential for more pronounced and adverse effects and make personalized decisions, as evidence based as possible in the holistic, considered, and optimal management of these patients.

DISCLOSURES

Author contributions: D.H. Vasant conceptualized the article, conducted a literature search, collected data, and wrote the manuscript. J.K. Limdi performed conceptualization, literature search, and manuscript review and provided critical intellectual content. S.P. Borg-Bartolo performed data collection and manuscript revision. A. Bonington and R. George wrote the manuscript and provided important intellectual content. R. George is the article guarantor.

Financial disclosure: None to report.

The patient is deceased and no next of kin could be reached, so informed consent was not obtained. All patient identifying information has been removed.

Acknowledgement: The authors would like to acknowledge Mrs J. Wrigley, who helped us retrieve the endoscopic images, and Dr M. Sapundzieski, who helped select the radiological images.

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