Granulomatosis with polyangiitis (GPA) is a systemic autoimmune anti-neutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis [1]. The typical clinical involvement of GPA entails the upper and lower respiratory tracts, and the kidneys. Other manifestations include musculoskeletal, ophthalmic, cutaneous and cardiac manifestations. Gastrointestinal involvement is uncommon and unless detected and treated promptly, may lead to life-threatening complications such as perforation.

We report a case of a 66-year-old man who presented with the common features of GPA and later developed intestinal perforation, following otherwise established treatment.

A 66-year-old male presented with mild abdominal pain and polyarthralgia of the knees and shoulders, beginning 10 days prior to his admission. His medical history included a year-long sensorineural hearing loss and recurrent rhinitis since childhood. Physical examination was unremarkable. Chest X-ray showed a solid opacity in the right lung hilum. Subsequent chest computed tomography (CT) scans confirmed the infiltration in the right lung lower lobe along with bilateral pulmonary nodules. Laboratory workup included elevated inflammation markers, with erythrocyte sedimentation rate (ESR) of 80 mm/h (range 0–35 mm/h) and a C-reactive protein (CRP) of 130 mg/dl (range 0–5 mg/dl). Creatinine was 0.8 mg/dl and urinary analysis findings were unremarkable.

The patient tested positive for ANCA using indirect immunofluorescence with cytoplasmic pattern (c-ANCA) +2 as well as by ELISA of anti-PR3 (proteinase 3) > 8 antibody index (normal range 0–0.99). Thus, a diagnosis of GPA was made and confirmed by a pathological examination of a lung biopsy, which revealed necrotizing vasculitis and a few giant cells. Immunosuppression was administered including high-dose prednisone (1 mg/kg/day) and cyclophosphamide (15 mg/kg every 2 weeks) adjusted to the patient’s age and renal function. On follow-up 4 weeks post-discharge, a favorable clinical and radiological response was noted in chest imaging and prednisone dosages were tapered down gradually.

Two months later, the patient was referred due to deterioration in renal function with creatinine 1.8 mg/dl. He presented with fever 39°C (102.2°F), diffuse abdominal pain, and a right dropped foot. Laboratory workup revealed leukocytosis (15,500/µl) and CRP of 185 mg/dl. A CT scan of the chest and abdomen and a renal ultrasound were unremarkable. Electrocardiogram showed right proximal peroneal and left ulnar neuropathies, consistent with mononeuritis multiplex. Renal function deterioration ensued, with a maximal creatinine level of 5.2 mg/dl. Urine sediment revealed red blood cell casts and dysmorphic red blood cells, consistent with glomerulonephritis. The following day, a positron-emission tomography/computed tomography (PET/CT) scan was performed to further elucidate the renal disease. The scan revealed diffuse bilateral uptake within the kidney’s parenchyma. Of note, these findings developed after continuous prednisone treatment for 3 months tapered down to a dose of 15 mg at the time of the PET/CT. Subsequent renal biopsy showed middle-sized arteritis with focal crescentic glomerulonephritis, compatible with pauci-immune glomerulonephritis. Accordingly, methylprednisolone was administered (1 g/day for three consecutive days) followed by 5 days of plasma exchange therapy. Concurrently, the patient experienced remarkable ongoing abdominal pain and intermittent signs of peritoneal irritation. Urgent abdominal CT scan revealed free gas adjacent to the distal small bowel. The patient underwent an urgent laparotomy that confirmed the CT scan findings, with a point perforation in the distal small bowel. One week later he underwent an acute re-laparotomy due to a second ileal perforation. Biopsy from surgery specimen showed necrotizing transmural acute and chronic arteritis consistent with GPA [Figure 1]. In the course of the postoperative period hemodialysis was initiated and a first course of rituximab (1000 mg) was administered. The patient eventually completed three courses of rituximab. Following significant clinical and serological improvement the colostomy was closed. Eighteen months post-diagnosis the patient was well, lived at home, and continued hemodialysis.
GPA involves mainly the upper and lower respiratory tracts and the kidneys. These are the classical clinical signs of GPA and a diagnosis is confirmed by biopsy. Gastrointestinal involvement is uncommon and the incidence in GPA is reported in 5–11% of patients. The clinical presentation is diverse and may include gingivitis, ulcerations, granulomatous inflammation of the gallbladder and pancreas, and intestinal perforations [2]. While the small intestine is the most common site of gastrointestinal involvement in GPA, intestinal perforation itself is a rare complication. Gastrointestinal involvement is typically a late manifestation of GPA, yet it may occur at any stage of the disease [3]. Although in our case the patient initially presented with mild abdominal pain, there were no findings on physical examination and the presenting pain subsided during the first 2 days after admission. Eventually, the patient had a late considerable gastrointestinal manifestation of GPA.

The renal involvement in GPA is diverse, ranging from asymptomatic hematuria to rapid progressive glomerulonephritis. The etiology of rapid progressive renal failure in our case was initially inconclusive, with a differential diagnosis of GPA, contrast-induced nephropathy, and induced interstitial nephritis. A PET/CT supported the diagnosis of GPA, with diffuse bilateral uptake within the kidney parenchyma. Generally, PET/CT is an effective imaging tool for identifying inflammatory processes. In vasculitides, it is mainly used for large-vessel vasculitis and is considered correlative with disease activity. In ANCA-associated vasculitis, the role of PET/CT has yet to be established. In 2014, a case-series showed accurate identification of organ involvement in GPA on PET/CT including confirmatory glomerulonephritis with bilateral FDG uptake [4]. These findings support the use of PET/CT in this case and demonstrate the potential diagnostic role of PET/CT in GPA patients prior to renal biopsy.

The mainstay therapy for newly diagnosed GPA is an immunosuppressive regimen of glucocorticoids and cyclophosphamide. Recently, rituximab has been considered an effective alternative to cyclophosphamide. Gastrointestinal manifestations may require additional immunosuppressive treatment.

Intestinal perforations are considered a medical emergency and are treated surgically. The majority of cases develop post-immunosuppressive therapy, as in this report. This finding may suggest that corticosteroids and immunosuppressive agents contribute to the development of intestinal perforations rather than the vasculitis activity itself. It can be difficult distinguishing between the two different processes. However, early onset perforations after treatment are perhaps more related to the immunosuppression whereas the detection of arteritis on biopsy is more decisive, such as in our case. In addition, there is no evidence in the literature regarding the benefits of switching immunosuppressive therapy once GI symptoms manifest.

Mortality rates are higher in GPA patients compared to the general population, and prognosis is even more unfavorable in the presence of gastrointestinal involvement [5]. Thus, a high index of clinical suspicion and proper imaging techniques are necessary for early treatment.

CONCLUSIONS
Our patient presented with the common manifestations of GPA that advanced and deteriorated to glomerulonephritis. PET/CT was used to help guide the diagnosis, which was established by renal biopsy. Eventually the patient developed an intestinal perforation, a rare life-threatening complication of the disease, despite being treated with the most appropriate therapy.

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Shiga toxin is a phage-encoded exotoxin that interrupts protein translation and functions as a virulence factor for enterohemorrhagic pathogen causing hemorrhagic colitis and acute renal failure. Havira et al screened a panel of EHEC mutants lacking various virulence factors to find those that interfered with inflammasome-mediated cell death. EHEC strains lacking Shiga toxin were more potent inducers of wild-type EHEC. Shiga toxin from wild-type EHEC interfered with pyroptosis by blocking the ability of the activated form of caspase-11, a cytoplasmic lipopolysaccharide sensor, to cleave gasdermin D and initiate the formation of gasdermin pores in the plasma membrane. This unanticipated activity of Shiga toxin provides EHEC with an additional means of evading the innate immune system.

Progressive brain disorder, is currently treated by infusion the cerebrospinal fluid every other week, which slows but does not halt progression of the disease. Sondhi and co-authors sought an alternative treatment using gene therapy. They injected an adeno-associated virus vector enabling expression of the normal human coding sequence for the CLN2 gene directly into the brain parenchyma of children with the disease. Progression of CLN2 was slowed in treated children but not to the same degree as in those treated with recombinant TPP1. Further improvements in gene therapy are needed before the progression of CLN2 disease can be halted.