A 60-year-old male with ulcerative colitis presenting with hypopharyngeal lesions

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Clinical history:

The patient is a 60-year-old gentleman with personal history of ulcerative colitis (UC) on tumor necrosis factor (TNF) antagonist infliximab. He initially presented with complaints of left-sided sore throat. CT scan of the neck described an asymmetric thickening of epiglottis and left aryepiglottic fold with focal enhancement. Flexible laryngoscopy revealed a papillomatous mass involving left arytenoid and extending towards the vocal cords, the biopsy of which revealed severe inflammation in absence of clear evidence of dysplasia. Several months later, the patient represented, this time with severe dysphagia and multiple mucosal lesions involving the left aryepiglottic fold and the hard palate. Together with the results of the previous biopsy, this presentation brought into question whether these lesions may constitute manifestations of Crohn's disease (CD) previously misdiagnosed as UC. The patient thus underwent panendoscopy with sampling of left-sided aryepiglottic fold, lateral pharyngeal wall, vallecula and soft palate.

Histology:

The histology again revealed benign squamous mucosa with prominent acute and chronic inflammation but no evidence of dysplasia (Fig. 1). Additionally, numerous foreign-body giant cells and nonnecrotizing granulomas were seen in all specimens. While morphological findings were reminiscent of CD, the differential of infectious etiology was investigated with spirochete immunohistochemistry as well as Ziehl-Neelsen, PAS and Gomori trichrome stains. While the former 3 were negative, the Gomori stain revealed scattered narrow-based budding organisms, both within and outside of macrophages (Fig. 2). No mycelial forms were identified.

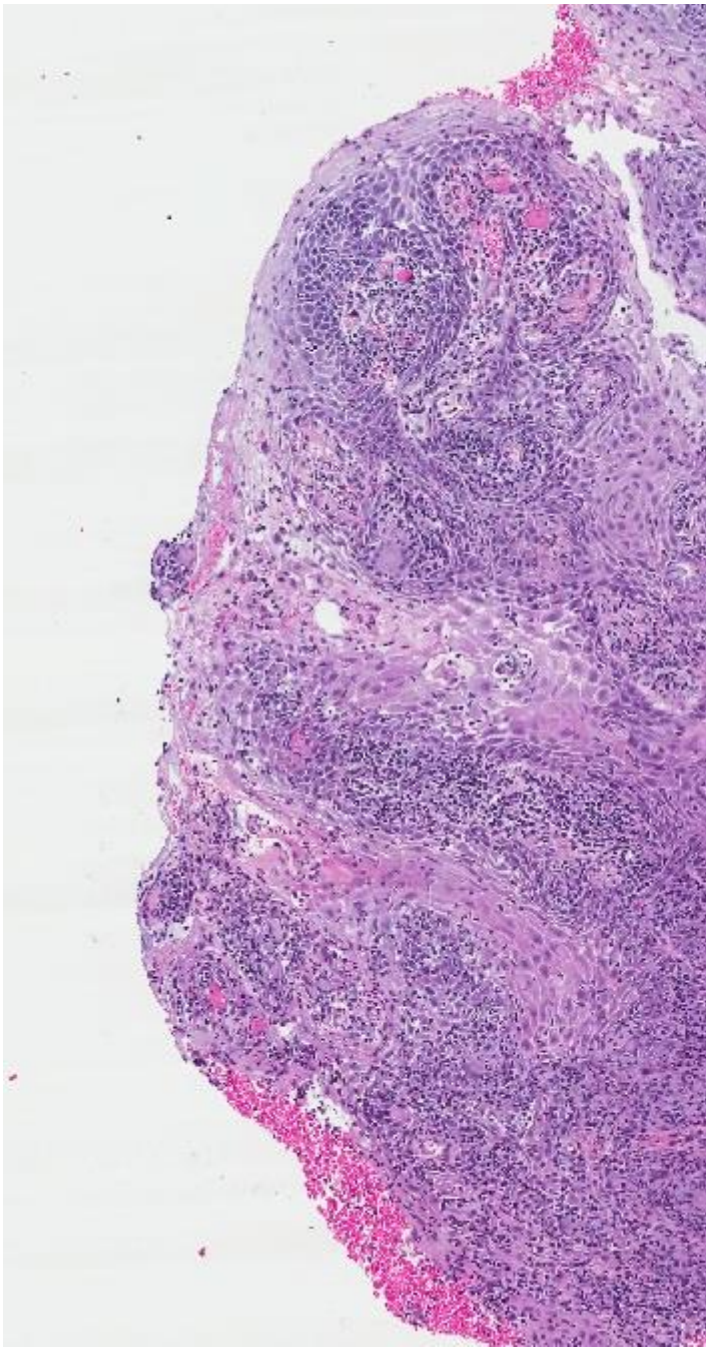

Fig. 1. A. Low magnification reveals squamous mucosa severely distorted by prominent acute and chronic inflammation. (H&E, 4X).

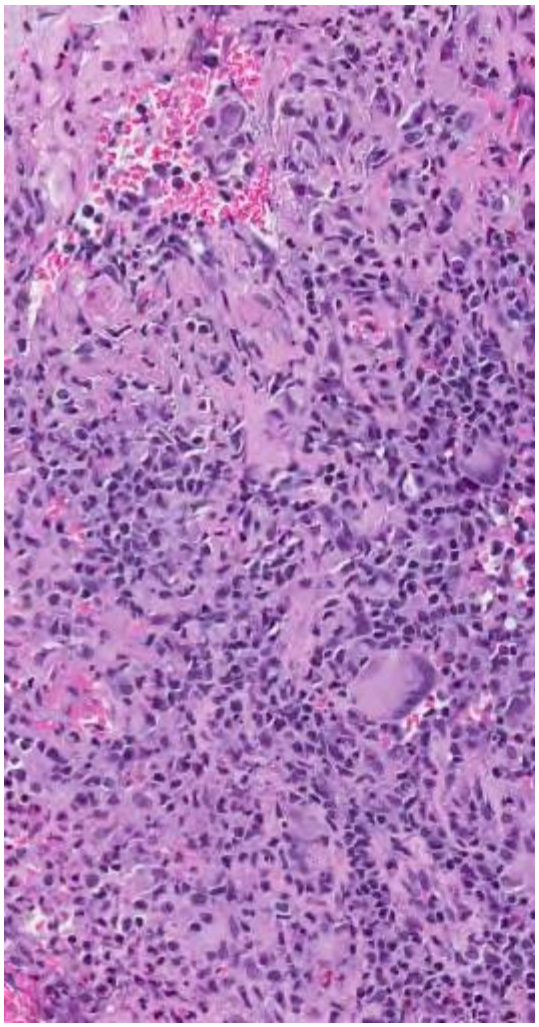

Fig. 1. B. Foreign-body giant cells and nonnecrotizing granulomas are seen (H&E, 10X).

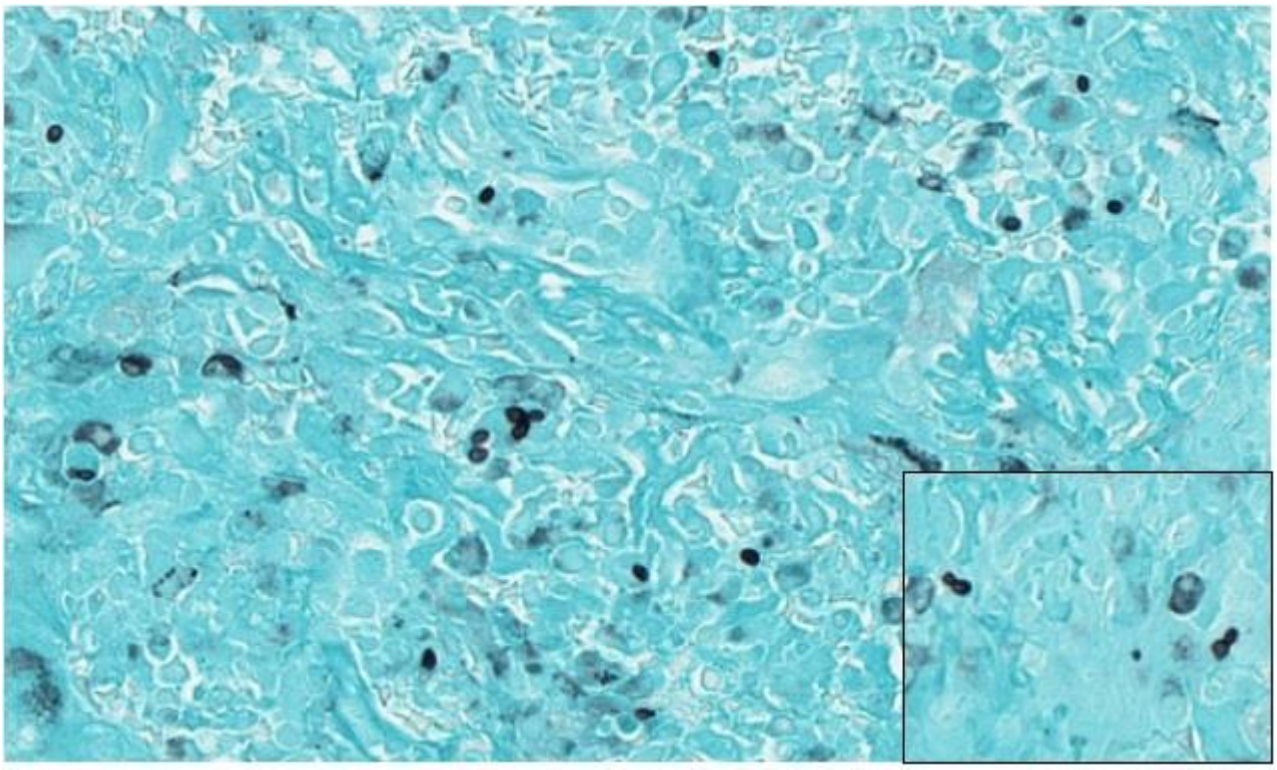

Fig. 2. Small ovoid narrow-based budding yeast forms are identified (Gomori trichrome stain, 40X).

Final Diagnosis: Fungal infection suggestive of *Histoplasma* spp.

Discussion:

TNF is a pleiotropic cytokine involved in multiple biological processes, including its role in host protection from infectious agents, as well as its impact on cellular proliferation, differentiation and apoptosis (1). In parallel, its pathogenic implication in several autoimmune conditions including inflammatory bowel disease (IBD) has been widely documented, although the exact molecular mechanisms are yet to be fully elucidated (2, 3). Therapeutic benefits of TNF inhibition in IBD have been demonstrated as early as in 1993 (4). TNF antagonists currently available for CD management include monoclonal antibodies infliximab and adalimumab, as well as PEG-conjugated Fab fragment, certolizumab (5). Given its critical role in host protection, it comes with no surprise that TNF inhibition is associated with increased incidence of opportunistic infections. More specifically, numerous reports of granulomatous diseases have been documented. In 2004, Wallis et al. (6) reviewed data from Adverse Event reporting System of the US Food and Drug Administration over 4.75-year period between 1998-2002, identifying 556 reports of granulomatous infections in 233,000 patients on infliximab evaluated (rate of 238.6 per 100,000 patients). The most commonly identified causative agent was *Mycobacterium tuberculosis* with a rate of 143.8 per 100,000 patients, in staggering comparison to 5.2-6.6 cases per 100,000 persons reported in United States for the corresponding years (7). Other pathogens included *Histoplasma capsulatum* (16.7 per 100,000 patients), *Candida* spp. (16.3 per 100,000 patients), *Listeria* spp. (15.5 per 100,000 patients), nontuberculous *Mycobacterium* spp. (12.9 per 100,000 patients), and *Aspergillus* spp. (12.4 per 100,000 patients).

Potentially challenging features in these patients include the fact that the infectious burden is variable and may be difficult to confirm histologically or immunohistochemically. Moreover, the underlying condition of these patients on its own can show overlapping morphological features. The head and neck manifestations of CD most commonly include oral lesions such as aphthae, ulcerations or edema, but laryngeal involvement has been described (8, 9). The biopsy often shows nonspecific chronic inflammation while the occasional deeply located nonnecrotizing granulomas can be missed on sampling.

The noninfectious differential diagnosis of granulomatous oropharyngeal lesions should likewise include granulomatosis with polyangiitis (Wegener's granulomatosis). While the diagnostic triad consists of vasculitis, granulomatous inflammation and necrosis, the histology is often nonspecific, limited to acute and chronic inflammation, and must be correlated with clinical and laboratory findings, including c-ANCA levels (9). Several other systemic autoimmune conditions may be considered in the appropriate clinical context, including Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis and vesiculobullous diseases. A history of vocal cord medialization should prompt a search for birefringent foreign material such as Teflon, silicone, Gore-Tex or titanium that can induce a variably prominent foreign body reaction (9). Finally, a minority of patients with sarcoidosis can have oropharynx and larynx manifestations, either as part of a systemic disease or as an exceedingly rare form of isolated involvement (9). Although nonspecific, Schaumann and asteroid bodies associated with nonnecrotizing granulomas can serve as morphological clues, while extensive necrosis or vasculitis should argue against the diagnosis.

In the present case, the clinical history of IBD and anti-TNF therapy helped narrow down the differential to CD and infectious etiology, with Gomori stain confirming the latter. The morphology is highly suspicious for histoplasmosis. The causative agent *H. capsulatum* can affect any part of the aerodigestive tract, and in larynx often presents as multiple lesions of nodular, ulcerated, granular or verrucoid appearance as described in this patient (9). Histologically, the small (2-5 μm) fungal organisms are usually seen within macrophages, in association with a lymphohistiocytic infiltrate and, occasionally, well-formed granulomas. The yeast forms show characteristic single small bud at a pointed pole that can be highlighted by PAS and Gomori stains, although the latter can be more useful for nonviable yeast in healed granulomas (10). This hypothesis was eventually confirmed by isolating *Histoplasma* from tissue cultures, although patient's serum and urine testing failed to reveal the presence of the specific antigen. In fact, it is useful to keep in mind that *Histoplasma* antigenemia and antigenuria varies with infectious burden and severity, and can frequently be negative in the context of a localized infection (11, 12), highlighting the importance of the histological diagnosis. In the current case, the patient was presumptively started on itraconazole following the biopsy results and the infection was successfully eradicated. At the last check-up 6 weeks after the diagnosis, the patient was doing well and his pain had diminished substantially.

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