Primary Esophageal Tuberculosis Without Dysphagia or Odynophagia in a Patient Without HIV

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ABSTRACT
We report a case of primary esophageal tuberculosis in a 35-year-old woman without HIV who presented with a month’s history of epigastric and chest pain without dysphagia or odynophagia and was found to have histologic evidence of multiple caseating granulomata on esophageal biopsy, which was confirmed positive for Mycobacterium tuberculosis complex DNA and cultures.

INTRODUCTION
Recent reports described tuberculosis (TB) as the leading cause of death from a single infectious disease agent globally. In the Philippines, it is the 6th leading cause of morbidity and mortality. Esophageal tuberculosis (ET) is believed to be a rare disease in both immunocompetent and immunocompromised individuals, and only 0.15% of patients who died of TB had esophageal involvement. However, in the past 2 decades, reports of ET have increased. Patients generally present with dysphagia and/or odynophagia, and sometimes with epigastric pain, chest pain, or hematemesis. There are 2 categories of ET: primary ET, which only involves the esophagus and is a less common finding, and secondary ET, which is an extrinsic manifestation of pulmonary TB. Of the several mechanisms proposed to explain secondary ET, direct extension of mediastinal and pulmonary TB or spinal TB is the most common. The other mechanisms for secondary ET, although uncommon, include contiguous seeding from lesions within the larynx or pharynx, spreading via the lymphatics, and hematogenous spread. One mechanism that suggests a primary ET transmission is swallowing of tuberculous saliva.

CASE REPORT
We present a case of primary ET in an otherwise healthy, 35-year-old woman without human immunodeficiency virus (HIV) from the Philippines who immigrated to Canada in 2007. Since immigrating to Canada, she has traveled back to the Philippines on a yearly basis. The patient presented with a 1-month medical history of epigastric and chest pain, which was worsened by food ingestion. She denied symptoms of dysphagia or odynophagia and constitutional symptoms. She did not have any known TB contacts. On physical examination, there was no cervical lymphadenopathy noted. The abdomen was soft without any palpable masses.

Initial investigations with an upper gastrointestinal contrast study revealed a well-circumscribed mass in the midesophagus along the left anterolateral wall with linear ulceration, which was concerning for malignancy. There was also spontaneous gastroesophageal reflux identified with features consistent with reflux esophagitis (Figure 1). Subsequently, an esophagogastroduodenoscopy was performed, which revealed a raised lesion that appeared to arise from the submucosal layer (Figure 2). It also revealed an area of central ulceration concerning for a dysplastic process (Figure 3). The lesion started at approximately 25 cm from the incisors and is estimated to be approximately 3 cm in length (25-28 cm). Multiple biopsies were taken from the lesion. Gastric biopsies were taken for the diagnosis of Helicobacter pylori.
Histopathologic report of the esophageal biopsies showed multiple caseating granulomata with a dense mixed inflammatory infiltrate rich in eosinophils (Figure 4). The gastric biopsies were negative for H. pylori. Fungal stains (Grocott methenamine silver and periodic acid Schiff) and culture of esophageal biopsy, as well as Ziehl-Neelsen and Warthin Starry stains and immunohistochemistry for herpes simplex virus and cytomegalovirus, were negative. There was no evidence of dysplastic changes. Overall, the histological features were highly suspicious for an infection, including TB, especially because the granulomata were caseating.

The definitive diagnosis of TB was confirmed with a nucleic acid test using the Xpert Mycobacterium tuberculosis complex (MTB)/resistance to rifampin polymerase chain reaction kit from Cepheid (Sunnyvale, CA). The DNA samples were positive for MTB. In addition, MTB was isolated using the automated system BACTEC (BD, Berkshire, United Kingdom) Mycobacteria Growth Indicator Tube and growth was detected after 12 days of incubation.

A thoracic x-ray was performed, which was reported as normal. This was followed by a thoracic computed tomography which did not show any evidence of mediastinal lymphadenopathy. HIV test was negative. She was started on a 6-month treatment regimen of quadruple therapy with isoniazid, rifampin, pyrazinamide, and ethambutol. The patient was clinically asymptomatic after 1 week of therapy.

**DISCUSSION**

The differential diagnoses for granulomata include infection, autoimmune (vasculitis, Crohn’s disease, and sarcoidosis), and drugs (Bacillus Calmette-Guerin vaccine and methotrexate). Some infectious causes of granulomata include M. tuberculosis, nontuberculous mycobacteria, and fungi (Histoplasma, Cryptococcus, Coccidioides, Aspergillus, and Blastomyces). Unlike Crohn’s disease and sarcoidosis (2 most frequent causes of granulomatous esophagitis), which are noncaseating, TB is a caseating granulomata. The patient had multiple caseating granulomata, which were confirmed to be MTB and diagnosed as TB.

A retrospective study of 24 patients with suspected ET revealed that 19 patients had definite ET and presented mostly with dysphagia (84%) and odynophagia (42%). Most recently, a case of primary ET was reported in a 25-year-old man who presented with progressive dysphagia, epigastric pain, and 10 kg weight loss over 8 months. Presentation of ET without dysphagia and/or odynophagia is a rare finding.
Among HIV-associated diseases, TB is the most common, causing the highest number of deaths worldwide.\textsuperscript{21} The classic symptoms of TB include productive cough, chest pain, shortness of breath, hemoptysis, fever, night sweats, and/or weight loss. These symptoms occur in patients with TB with or without HIV.\textsuperscript{21} In addition, many patients infected with HIV with TB are less likely to have pulmonary cavitation than patients with only TB, whereas some patients infected with HIV with pulmonary TB have normal chest radiograph.\textsuperscript{22–24} Others have indicated that patients with HIV are more likely than patients without HIV to have extrapulmonary TB, with or without concomitant pulmonary disease.\textsuperscript{21,25} Extrapulmonary TB commonly occurs in the pleura, abdomen, central nervous system, lymphatic system, and skeletal system.\textsuperscript{26,27} Our patient was HIV negative and presented with no classic symptoms of TB except for chest pain. She had no radiographic findings of pulmonary TB but had an extrapulmonary TB finding in a rare site, the esophagus.

Because our patient did not have detectable evidence of pulmonary TB, it is reasonable to conclude that ET did not seed from other sites but was rather swallowed, suggesting a diagnosis of primary ET. It is unclear how this would occur considering the fact that the esophageal transit time is likely inadequate for the infectious agent to attach to the squamous epithelial mucosa of the esophagus unless there was a disruption of the esophageal mucosal or delayed esophageal clearance.\textsuperscript{14} This case study adds to the bulk of evidence supporting unusual presentations of primary ET and warrants the need to include ET as one of the differential diagnoses for epigastric and chest pain, especially in patients with risk factors for TB. Although reflux esophagitis could account for the epigastric pain experienced by our patient, it is reasonable to have a broad differential that includes ET in patients presenting with epigastric and chest pain so as to not miss a possible case of ET.

**DISCLOSURES**

Author contributions: H. Ogbomo wrote the manuscript. A. Thiesen provided pathology slides and reviewed the manuscript. S. Zepeda-Gomez reviewed and edited the manuscript. A. Kohansal-Vajargah provided esophagogastroduodenal images, reviewed and edited the manuscript, and is the article guarantor.

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