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Esophageal Carcinoma Cuniculatum Associated with Non-Necrotizing Granulomatous Inflammation and Lymphadenopathy: Clinicopathologic Features and Diagnostic Challenges

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: **Male, 52**
Final Diagnosis: **Carcinoma cuniculatum**
Symptoms: **Chest discomfort • dysphagia**
Medication: —
Clinical Procedure: —
Specialty: **Gastroenterology and Hepatology**

Objective: **Rare disease**
Background: Esophageal carcinoma cuniculatum (CC) is an exceptionally rare, well-differentiated squamous cell carcinoma (SCC) with initial microscopic evaluation often yielding inconclusive diagnoses due to its characteristically bland histomorphologic appearance on superficial endoscopic biopsy. This can lead to delayed diagnosis and pose challenges in further management of these cases.

Case Report: We present the case of a 52-year-old man with symptoms of dysphagia and odynophagia. The initial chest CT scan showed gastroesophageal (GE) junction wall thickening and regional lymphadenopathy. Esophagogastroduodenoscopy (EGD) revealed an esophageal mass, but the mucosal biopsies were inconclusive. Repeat endoscopic biopsies also failed to yield a definitive diagnosis. Under strong clinical suspicion for malignancy, an esophagogastrectomy was performed, which yielded the diagnosis of CC, and the associated enlarged lymph nodes revealed non-necrotizing granulomatous lymphadenitis.

Conclusions: Only 15 cases of esophageal CC have been described in the literature. This particular case is unique due to the associated abundant lymphoplasmacytic and granulomatous inflammation and involvement of regional lymph nodes by non-necrotizing granulomas not previously described.

MeSH Keywords: **Carcinoma, Squamous Cell • Esophagus • Immunoglobulin G**

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Background

Carcinoma cuniculatum (epithelioma cuniculatum) is a unique variant of extremely well-differentiated SCC originally established in the plantar skin surface and first described by Aird et al. in 1954 [1]. The pathognomonic histopathologic feature is well-differentiated squamous epithelium with minimal atypia that form deep, keratin-filled channels extending into the tissue. Additionally, features of hyperkeratosis, dyskeratosis, paradoxical keratinization, acanthosis, intraepithelial neutrophilic inflammation and microabscesses, and koilocyte-like cells are consistently visualized [2]. Since 1954, CC has been subsequently identified in various non-cutaneous mucosal sites such as the oral cavity and larynx. The 2 earliest esophageal CC cases were only recently recognized in the literature in 2005 [3], with merely 13 additional cases published to date [2,4–6]. In this report, we present the case of a 52-year-old man with esophageal CC with extensive lymphoplasmacytic and non-necrotizing granulomatous inflammation and regional lymph nodes revealing non-necrotizing granulomatous lymphadenopathy, which has never been previously described.

Case Report

Clinical course

A 52-year-old man with a past medical history significant for a 90 pack-year smoking history and reflux esophagitis initially presented to an outside hospital with 2 months of dysphagia and chest discomfort. Workup included an initial chest CT scan that revealed poorly defined esophageal wall thickening at the gastroesophageal (GE) junction with regional mediastinal lymphadenopathy suspicious for malignancy. Subsequent upper endoscopy confirmed an esophageal mass. However, superficial biopsies taken from the mass were indeterminate for malignancy and his care was then transferred to our institution for further workup. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and 2 additional sets of esophageal mass biopsies, including a snare excision of a protuberant portion of the mass measuring 1.5×1.2×0.9 cm in diameter, were subsequently performed and all failed to yield a definitive diagnosis. The 18F-FDG PET/CT was interpreted as showing a “partially obstructive distal esophageal carcinoma with infiltrative wall thickening and mediastinal adenopathy”. Multiple foci of ground-glass and nodular airspace opacity were identified, which were regarded as consistent with respiratory bronchiolitis in the context of smoking. No abnormal activity was identified in the abdomen. Three months after his first set of biopsies and under persistent strong clinical suspicion of malignancy, he underwent surgical resection (esophagogastrectomy), ultimately revealing histopathologic features of CC. He continues to feel well without symptoms of dysphagia at over 1 year after his diagnostic and therapeutic surgery.

Endoscopic findings

EGD examination revealed a papillary, nodular deformity noted in the distal esophagus (Figure 1A). In the region of the deformity, endoscopic ultrasound (EUS) showed a dramatically abnormal esophageal wall with only a faintly visible muscularis propria, loss of all other sonographic layers, and clearly visible hypoechoic tissue extending through the muscularis propria into the surrounding adventitia (Figure 1B). Involvement extended with a thick pedicle to adjacent, irregularly thickened parietal pleura, and more than 7 regional lymph nodes were enlarged and sonographically suspicious for malignancy. The appearance of the esophageal wall suggested an intrinsic esophageal mass rather than extrinsic esophageal involvement by a primary lymph node disorder. The endoscopic and sonographic appearances were not felt to be consistent with chronic granulomatous infection such as histoplasmosis or the rare published reports of esophageal involvement in sarcoidosis [7]. The preliminary staging based on these findings was T4aN3M0 (vs. NO pending cytology).

Gross findings

The esophagogastrectomy specimen consisted of a distal esophagus (3.7 cm in length) with attached proximal stomach (16.8 cm in length). The GE junction was clearly demarcated and showed a tan-yellow raised papillary mass, 1.0 cm in greatest dimension, with a central white friable area and invasion into the underlying submucosa (Figure 1C). Proximal to this mass within the esophagus were 6 nodular portions of raised mucosa ranging from 0.3 cm to 0.7 cm in greatest dimension, with 1 nodule having an ulcerative surface. All nodules appeared grossly confined to the mucosa.

Six paraesophageal and 18 paragastric lymph node specimens were also obtained, which were up to 1.9 cm in greatest diameter.

Microscopic findings

Microscopic examination of the endoscopic mucosal biopsies revealed fragments of predominantly bland squamous epithelium with mild cytologic atypia and focal papillomatous configuration. Marked lymphoplasmacytic infiltrate and prominent lymphoid follicles with occasional non-necrotizing granulomas were identified on subsequent biopsies (Figure 2A). EUS-FNA smears showed abundant neutrophils and occasional squamous cells with mild-to-moderate cytologic atypia, but failed to yield a definite diagnosis of carcinoma (Figure 2B).

Microscopic examination of the mass showed a tumor with infiltrative borders and deep endophytic channels, sinuses, and crypts lined by well-differentiated squamous cells (Figure 2C)

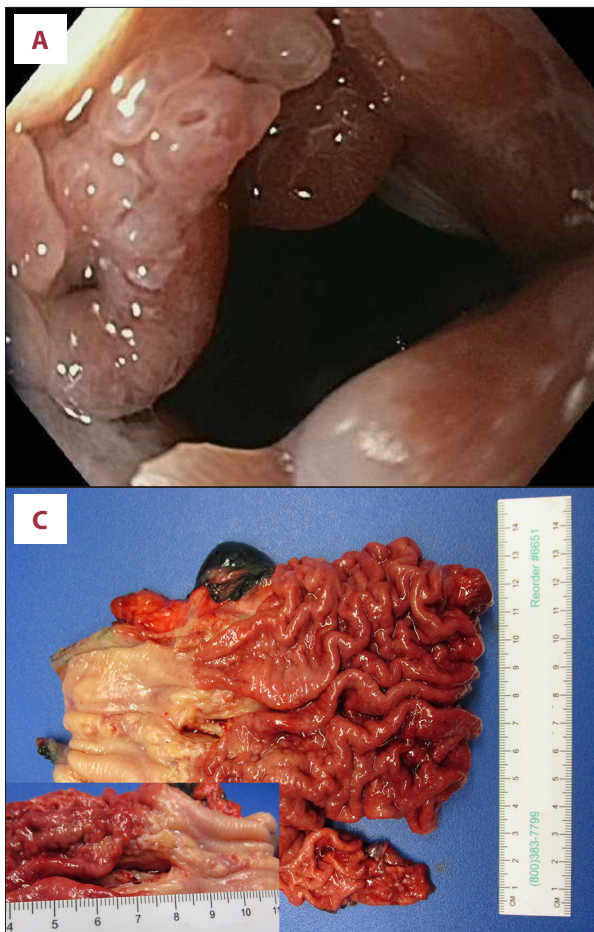


Figure 1. Endoscopic ultrasound (EUS) and gross images of CC. (A) Endoscopic image of distal esophagus revealing a prominent polypoid papillary-like lesion with distal satellite lesions; (B) EUS image showing only a faintly visible muscularis propria, loss of all other sonographic layers and clearly visible hypoechoic tissue extending through the muscularis propria into the surrounding adventitia; (C) Gross image of esophagogastric specimen showing lesion located in the distal esophagus at the gastroesophageal junction.

invading deeply into the muscularis propria, consistent with the esophageal wall abnormality noted on the ultrasonography. Neutrophilic microabscesses were present within keratin-filled crypts and occasional ruptured sinuses elicited an intense chronic inflammation with foreign body-type giant cell reaction. The neoplastic squamous epithelium was mostly bland-appearing with focal cytologic atypia most pronounced in the areas of this chronic inflammation. Dyskeratosis, areas of prominent koilocytic changes and paradoxical keratinization of the neoplastic squamous epithelium, was also noted (Figure 2C–2E). The stroma surrounding the tumor was remarkable for markedly dense lymphoplasmacytic infiltrate. All margins were uninvolved by invasive carcinoma, with the closest margin 5.2 cm from the invasive carcinoma. In the adjacent uninvolved proximal esophagus, dense Crohn's-like transmural lymphoplasmacytic infiltrate with non-caseating epithelioid granulomas and giant cells were seen. Rare lymphoid aggregates with epithelioid granulomas were noted in the stomach. Lymphovascular or perineural invasion was not identified. Twenty-two lymph nodes were negative for metastatic carcinoma, with most revealing non-necrotizing granulomas (Figure 2F). The tumor was designated pathologic stage pT2N0.

GMS performed on distal esophagus EUS FNA was negative for organisms. AFB stain on perigastric lymph node was negative for acid-fast organisms. CD3, CD20, and kappa and lambda light-chain immunohistochemical stains showed no evidence of lymphoproliferative disorder. There was no increase in IgG4-positive plasma cells to support the diagnosis of IgG4-related disease.

Discussion

Carcinoma cuniculatum is a rare variant of well-differentiated squamous cell carcinoma first identified in the plantar skin with subsequent non-cutaneous locations identified. Only 15 cases of esophageal CC are described in the literature. Diagnosis of CC on endoscopic biopsy is particularly challenging due to its characteristically bland histomorphology. In fact, none of the 15 cases reported in the literature were diagnosed by mucosal biopsies. Two cases were diagnosed by endoscopic mucosal resection specimens (EMR) [4], while the remaining cases, including ours, were managed by surgical resection both for diagnosis and treatment [2,3,5]. In fact, our patient endured 3 sets of biopsies and an EUS-FNA over a span of 3 months, without definitive diagnosis of malignancy.

In an attempt to make the diagnosis of CC possible on a biopsy specimen, Chen et al. [4] used a numerical tally system of the common histomorphologic features seen in CC, including:

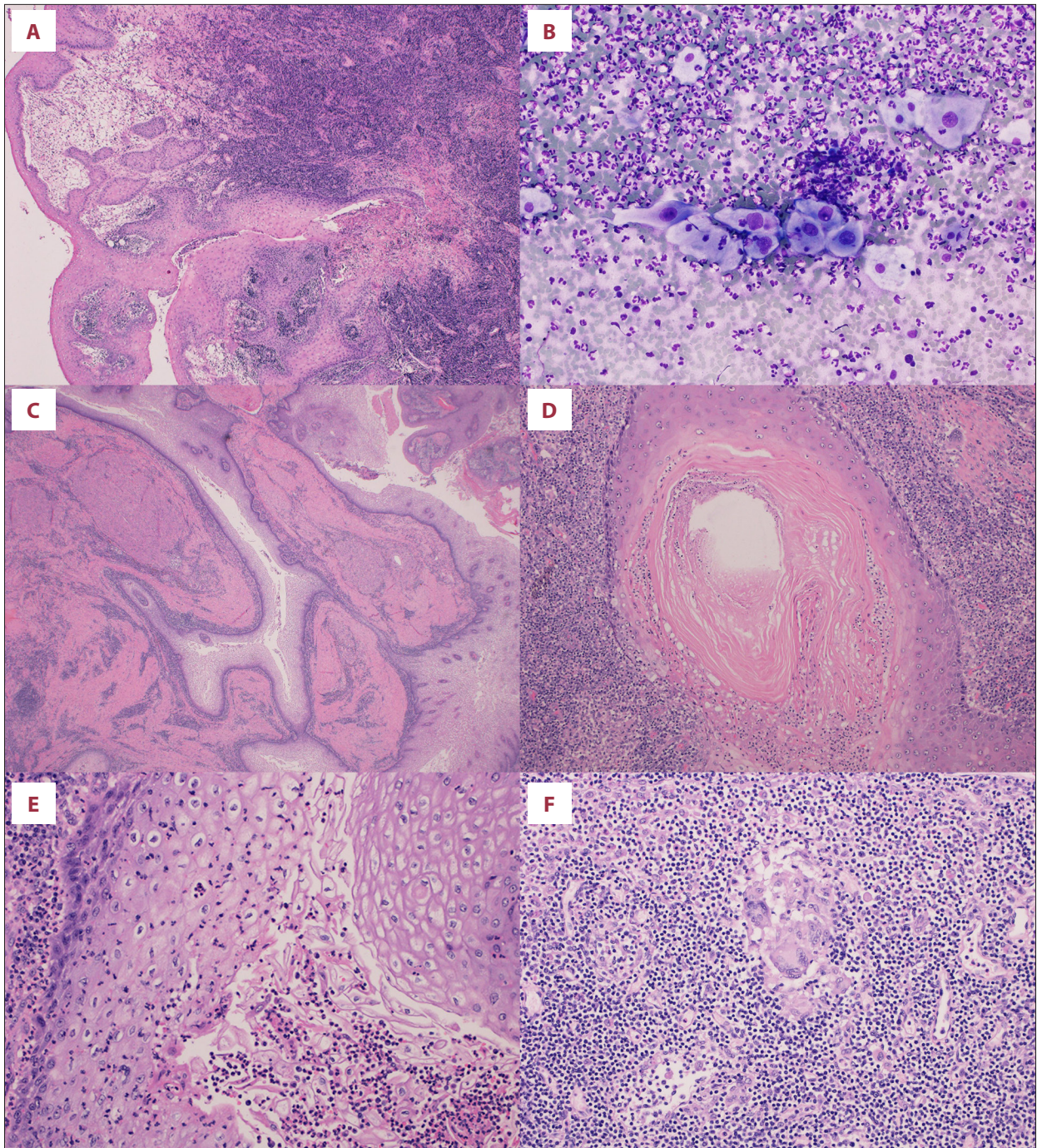


Figure 2. Microscopic features of CC on biopsy, EUS-FNA and resection specimens. (A) Superficial endoscopic biopsy of the mass showing relatively bland squamous proliferation with crypt formation and associated abundant chronic inflammation (H&E, 4x). (B) EUS-FNA smear revealing moderate cytologic atypia of squamous cells and acute inflammation (DiffQuik, 40x). (C) Low power view of resected tumor revealing deep crypts and burrows lined by acanthotic squamous epithelium (H&E, 2x); (D) Keratin filled crypt with paradoxical keratinization and parakeratosis (H&E, 10x); (E) Neutrophilic microabscess, intraepithelial neutrophils and on the top left side koilocyte-like squamous cells (H&E, 20x); (F) Regional lymph node with non-necrotizing granuloma (H&E, 20x).

(1) acanthosis, (2) dyskeratosis, (3) hyperkeratosis, (4) paradoxical keratinization, (5) neutrophilic microabscesses, (6) intraepithelial neutrophils, (7) focal cytologic atypia, (8) koilocyte-like cells, and (9) keratin-filled cysts or burrows. Each histologic feature of CC was equally weighted. The authors concluded that if at least 7 of these features were present, the diagnostic sensitivity in mucosal biopsies of CC was significantly improved, with a specificity of 100%. The presence of 5 or 6 features, however, still warrants close clinical follow-up, since many of these biopsies carried the diagnosis of active esophagitis, which is associated with development of squamous cell carcinoma. Our patient presented with a similar scenario, having a history of reflux esophagitis and multiple mucosal biopsies consistently revealing 5 or 6 out of the 9 features and specifically lacking intraepithelial neutrophils, neutrophilic microabscesses, keratin-filled cysts or burrows, and significant cytologic atypia.

Although the diagnostic route of CC can be arduous and exacerbated with surgical resection complications from deeply invasive tumors, the tentative prognosis appears to be quite favorable according to the 9 esophageal CC case reports published by Landau et al. [2]. Seven of the patients were followed for a median duration of 84 months with no disease recurrence, while 2 died shortly after surgery due to postoperative complications. Two additional CC publications [3,5] show no recurrence or metastases after a relatively modest follow-up of 14 months. However, in another study by Chen et al., in which 2 patients underwent EMR with radiation instead of the typical surgical resection [4], the prognosis is less certain. One of these patients experienced tracheal recurrence and died 2 months following radiation therapy. In our case, 15 months post-operatively, the patient is symptom-free and a follow-up CT of the chest revealed no definite evidence of disease recurrence or metastasis.

As described in previous case reports [2,3,5], prominent stromal lymphoplasmacytic infiltration, particularly surrounding the keratin-filled crypts, was identified in our patient's resection specimen and was also noted on the endoscopic mucosal biopsies, which led to the consideration of IgG4-related disease (IgG4-RD). IgG4-RD is an immune-mediated fibroinflammatory condition manifesting as 'pseudotumors' that mimic cancer; it is characterized histopathologically by dense lymphoplasmacytic infiltration and IgG4-positive plasma cells, and results in storiform-patterned fibrosis [8,9]. There is essentially ubiquitous involvement of organ systems, although only a few cases of the esophagus have been reported [10–14] with consistent clinical features of dysphagia, weight loss [13], and suspicion for malignancy on EGD [13,14]. Although our patient did not exhibit storiform-patterned fibrosis on histology, we sought to rule out IgG4-RD based on the clinical presentation and the extreme rarity of both CC and IgG4-RD. An immunohistochemical

stain for IgG4, however, did not reveal any significant increase in IgG4-positive plasma cells. In addition to IgG4-RD, the lymphoid proliferation was also concerning for a lymphoproliferative disorder. Of note, lymphomas may actually resemble IgG4-RD histopathologically but can be differentiated by clonality studies [9]. The presence of polytypic plasma cells highlighted with both kappa and lambda light-chain immunostains ruled out lymphoproliferative disorders in our patient. As mentioned above, a similar inflammatory infiltrate was observed by others in a few cases of esophageal CC near intact or ruptured cysts, with an exaggerated stromal inflammatory response containing lymphocytes, plasma cells [5], histiocytes, and occasional eosinophils [2]. The possibility of IgG4-RD was not mentioned in those case reports. Although the etiology of the lymphoplasmacytic infiltrate is not entirely clear, it probably represents a reaction to paradoxical keratinization occurring in deeply invasive channels and crypts.

Beyond the exceedingly rare occurrence of esophageal CC, the present case is of additional interest due to some unique histopathologic findings. First, peritumoral and extra-tumoral (Crohn's-like) lymphoid aggregates with non-necrotizing granulomas were present and also noted in the adjacent esophagus and stomach. Secondly, sarcoid-like lesions were identified in multiple regional lymph nodes. To the best of our knowledge, neither of these findings has been described previously in any CC in the literature. Crohn's-like lymphoid aggregates have been described in various carcinomas, although most are recognized in a subgroup of colorectal carcinoma deficient in mismatch repair enzyme expression [15] and they have been associated with esophageal squamous cell carcinoma [16]. Both peritumoral and Crohn's-like lymphoid aggregates may represent an immune reaction against the tumor, described as tertiary lymphoid organs (TLOs). TLOs are induced postnatally in non-lymphoid tissues in response to various triggers, including inflammation, infection, and solid tumors; and may carry a favorable prognosis. TLOs are thought to provide important lymphocytic functional environments for both cellular and humoral immunity and are similar to lymph nodes or Peyer's patches in terms of function and structure [17].

Sarcoid-like reactions, as seen in our case with no clinical history of sarcoidosis, are granulomas consisting of an epithelioid-cell aggregate bordered by lymphocytes, morphologically identical to sarcoidosis. They occur infrequently, may hold prognostic significance, and are found in variable sites, including within the tumor, regional and draining lymph nodes, and even distant locations from the tumor site [18,19]. The granulomas differ in magnitude depending on the specific tumor's combination of antigenic properties [18]. Consequently, the sarcoid-like reaction itself may cause enlarged lymph nodes to erroneously appear malignant. The pathogenesis is thought to be due to tumorigenic antigens that create an immunologic

cell-mediated response leading to the formation of a nonspecific granulomatous reaction [19]. A literature review of sarcoid-like reactions in malignant tumors by Brinker in 1986 revealed that sarcoid-like reactions occur predominantly in carcinomas and, of the solid tumors, may represent a greater proportion of squamous cell carcinomas than adenocarcinomas [19].

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Conclusions

In conclusion, we describe a rare case of esophageal CC with multiple indeterminate superficial mucosal biopsies resulting in a diagnostic dilemma, but a strong clinical suspicion of malignancy led to radical esophagogastrectomy, yielding the diagnosis of CC with associated peritumoral Crohn's-like lymphoid aggregates and sarcoid-like reaction involving the regional lymph nodes, possibly representing a secondary immune reaction.