REPORTE DE CASO

From presumed metastasis to infection: coccidioidomycosis mimicking metastatic gastroesophageal adenocarcinoma

De metástasis a infección: Coccidiomicosis imitando adenocarcinoma esofágico metastásico

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ABSTRACT
Early gastroesophageal junction (GEJ) cancer commonly presents without distant disease. The development of locoregional lymphadenopathy and acute pulmonary embolism raises concern for metastatic disease and may lead to inappropriate upstaging if not properly investigated. We present a 51-year-old immunocompetent Hispanic man with newly diagnosed T1a GEJ adenocarcinoma who developed FDG-avid mediastinal lymphadenopathy and an incidental subsegmental pulmonary embolism on staging computed tomography. Histological sampling via endobronchial ultrasound-guided fine needle aspiration revealed granulomatous inflammation without malignancy. Further workup confirmed an acute Coccidioides lymphadenitis. The patient was successfully treated with fluconazole 400 mg daily for three months, with complete radiological and endoscopic resolution. This case underscores the critical importance of histological confirmation of lymphadenopathy before attributing it to metastatic disease in early-stage GEJ cancer. Failure to consider infectious etiologies, particularly coccidioidomycosis in endemic areas or in patients with travel history, may result in unnecessary upstaging, inappropriate treatment escalation, and avoidable harm.
Keywords: *Coccidioidomycosis; Lymphadenitis; Esophagogastric Junction; Neoplasm Staging; Lymphadenopathy (source: MeSH NLM).*

RESUMEN
El cáncer de la unión gastroesofágica (UGE) en estadios tempranos se presenta comúnmente sin enfermedad a distancia. El desarrollo de linfadenopatía locorregional y embolia pulmonar aguda en estos casos genera la sospecha de enfermedad metastásica y puede conducir a una sobreestadificación inapropiada si no se investiga adecuadamente. Presentamos el caso de un hombre hispano de 51 años, inmunocompetente, con diagnóstico reciente de adenocarcinoma de la UGE en estadio T1a, quien desarrolló linfadenopatía mediastínica FDG-ávida y una embolia pulmonar subsegmentaria incidental en la tomografía computarizada de estadificación. La biopsia mediante ultrasonido endobronquial con aguja fina reveló inflamación granulomatosa sin evidencia de malignidad. Estudios complementarios confirmaron linfadenitis aguda por Coccidioides. El paciente fue tratado exitosamente con fluconazol 400 mg diarios durante tres meses, con resolución radiológica y endoscópica completa. Este caso subraya la importancia crítica de la confirmación histológica de la linfadenopatía antes de atribuirla a enfermedad metastásica en el cáncer de la UGE en estadio temprano. La omisión de etiologías infecciosas, especialmente coccidiomicosis en áreas endémicas o en pacientes con antecedentes de viaje, puede resultar en sobreestadificación innecesaria, escalada de tratamiento inapropiada y daño evitable.
Palabras clave: *Coccidiomicosis; Linfadenitis; Unión Esofagogástrica; Estadificación de Neoplasias; Linfadenopatía (fuente: DeCS Bireme).*

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INTRODUCTION

Coccidioidomycosis often presents as pulmonary disease. Isolated lymphadenopathy without respiratory involvement, particularly in immunocompetent individuals, is exceedingly rare and poses a substantial diagnostic challenge, especially when it occurs in the context of a concurrent malignancy. Early-stage gastroesophageal junction (GEJ) adenocarcinoma carries a low risk of locoregional or metastatic spread at diagnosis, and venous thromboembolism (VTE) at presentation is also uncommon in early disease. When these findings co-occur, the clinical gestalt can be misleading and steer clinicians toward a presumptive diagnosis of metastatic disease, with potentially harmful consequences for the patient.

We describe a case of isolated Coccidioides lymphadenitis in an immunocompetent patient without pulmonary involvement, accompanied by an incidental pulmonary embolism, in the context of T1a GEJ adenocarcinoma. This case illustrates the risks of premature diagnostic closure and highlights the indispensable role of histological confirmation before staging decisions are finalized.

CASE REPORT

A 51-year-old Hispanic man was referred to our practice for an incidental diagnosis of a GEJ mass detected on esophagogastroduodenoscopy (EGD), performed at patient's request concurrently with a screening colonoscopy. The lesion was removed piecemeal by endoscopic mucosal resection (EMR) with histopathology demonstrating moderately-to-poorly differentiated intramucosal adenocarcinoma (T1a) with negative deep margins and absence of lymphovascular invasion.

Computed tomography (CT) of the chest, abdomen, and pelvis performed for staging revealed a subsegmental pulmonary embolism in the posterior right lower lobe as well as an enlarged right lower paratracheal lymph node. Positron emission tomography (PET) scan (Figure 1) demonstrated multiple mediastinal fluorodeoxyglucose (FDG)-avid lymph nodes, raising strong concern for metastatic disease.

Given the discordance between the early pathological stage (T1a) and the imaging findings, a recognized red flag warranting tissue confirmation rather than empirical upstaging, the patient underwent endobronchial ultrasound (EBUS) with fine needle aspiration (FNA) (Figure 2). Pathology revealed granulomatous inflammation with no evidence of malignancy. Bronchoscopy with bronchoalveolar lavage (BAL) grew saprophytic fungus on fungal culture. Immunodiffusion testing was consistent with acute Coccidioides infection (positive IgM only). The patient was diagnosed with coccidioidal lymphadenitis and treated with a 3-month course of fluconazole 400 mg daily. Subsequent immunodiffusion testing and PET scan demonstrated complete resolution of abnormalities (Figure 3). The patient also completed three months of anticoagulation with apixaban for the incidental pulmonary embolism. Multiple surveillance endoscopies and endoscopic

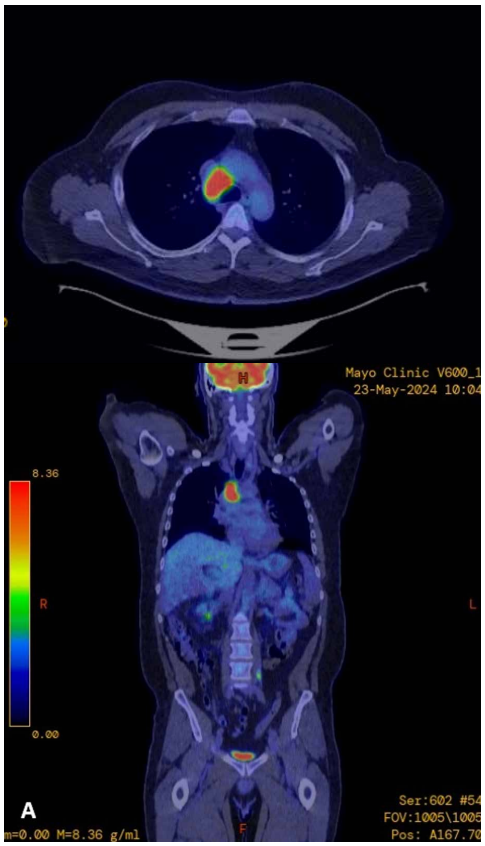

Figure 1. FDG-PET/CT comparison before antifungal treatment for coccidioidal lymphadenitis. Baseline FDG-PET/CT demonstrating intensely FDG-avid right paratracheal and precarinal lymphadenopathy (SUVmax 15.5), initially interpreted as malignant-appearing thoracic lymphadenopathy in the setting of newly diagnosed T1a gastroesophageal junction adenocarcinoma.

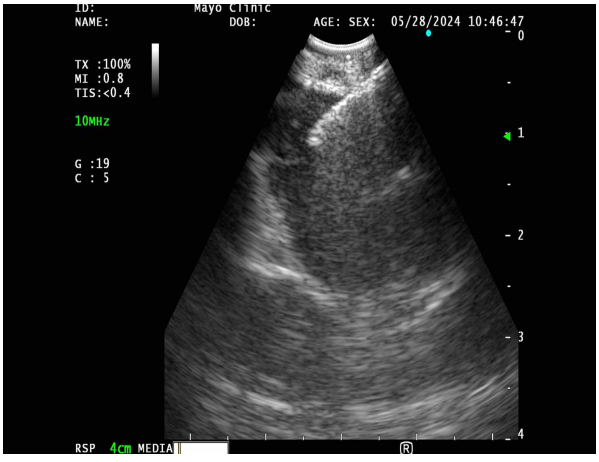

Figure 2. Targeted station 4R EBUS + FNA based on the PET scan.

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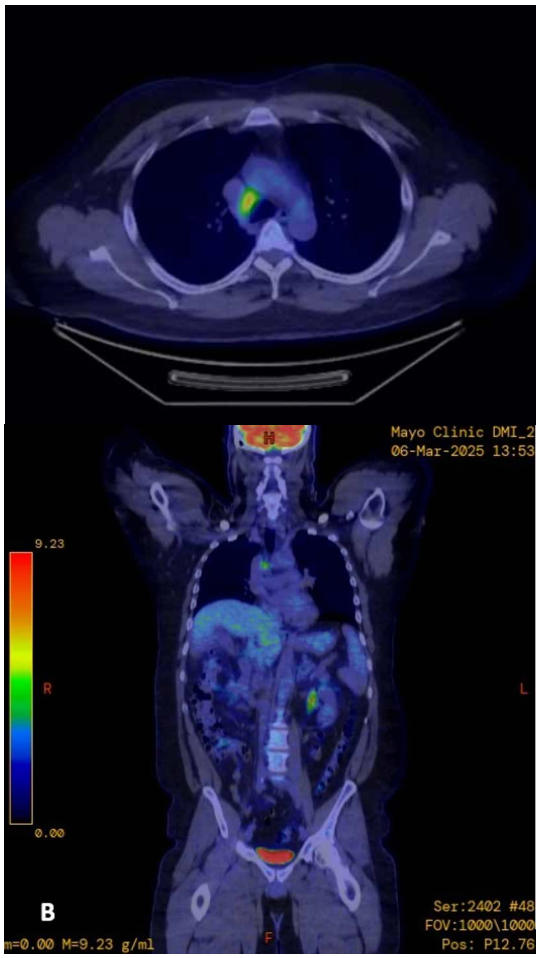

Figure 3. FDG-PET/CT comparison after antifungal treatment for coccidioidal lymphadenitis. Follow-up FDG-PET/CT after completion of a 3-month course of fluconazole. There is interval decrease in both size and metabolic activity (SUVmax from 15.5 to 8) of the right paratracheal lymph nodes, consistent with treatment response. Yellow arrows indicate the dominant right paratracheal lymph node conglomerate on each study.

ultrasounds confirmed complete eradication of the GEJ malignancy with no evidence of recurrence.

DISCUSSION

This case illustrates a critical pitfall in gastrointestinal oncology: the premature attribution of lymphadenopathy to metastatic disease without histological confirmation. The combination of FDG-avid mediastinal nodes and an incidental pulmonary embolism in a patient with a newly diagnosed GEJ cancer created a compelling but ultimately misleading clinical picture of advanced disease.

Low metastatic risk in T1a GEJ adenocarcinoma

Early-stage GEJ adenocarcinoma is associated with a very low risk of locoregional and distant spread. Multiple studies consistently report that the risk of lymph node metastasis for intramucosal esophageal adenocarcinoma (T1a) is approximately 1-4% [1,2]. In a landmark study by Stein et al., no lymph node metastases were found in patients with intramucosal cancer, in contrast to those with submucosal disease, likely due to limited access to deeper lymphovascular channels [3]. A recent meta-analysis showed a 4.2% rate of nodal metastasis in T1a disease, with individual case series reporting rates between 1% and 5% [4]. The risk increases only modestly with poor differentiation or larger tumor size but remains low overall [5]. This biological context is essential: mediastinal lymphadenopathy in T1a GEJ cancer should prompt investigation of alternative etiologies before any assumption of metastatic disease.

Red flags and indications for lymph node biopsy

Clinicians evaluating lymphadenopathy in early-stage GEJ cancer should consider histological sampling when the following features are present: (1) a significant discordance between the low pathological risk of the primary tumor (e.g., T1a, no lymphovascular invasion) and the extent of nodal involvement on imaging; (2) lymph node distribution atypical for the primary tumor's drainage pattern (e.g., mediastinal nodes with a distal GEJ primary); (3) morphological characteristics on PET/CT suggesting an alternative diagnosis, such as absence of central necrosis, which favors non-necrotizing granulomatous processes such as coccidioidomycosis or histoplasmosis over malignancy [6,7]; and (4) any relevant epidemiological context, including residence in or travel through endemic regions for fungal infections (e.g., southwestern United States for Coccidioides) [8]. In our case, all four features were present, and tissue diagnosis was appropriately pursued.

Coccidioidal lymphadenitis as a diagnostic mimic

Coccidioidomycosis is caused by the dimorphic fungi Coccidioides immitis and Coccidioides posadasii, endemic to the arid regions of the southwestern United States, northern Mexico, and parts of Central and South America. Infection is generally asymptomatic in immunocompetent individuals, with symptomatic pulmonary disease occurring in approximately 40% of cases [8]. Disseminated disease occurs in roughly 1% of all infected individuals; lymph node involvement, though possible, is not the most frequent site of extrapulmonary spread, skin, bone, and the central nervous system are more commonly affected [9-11].

Isolated lymphatic involvement by Coccidioides without evident pulmonary disease, as seen in our patient, is rare. We presume that an acute, subclinical pneumonic episode preceded lymphatic dissemination, consistent with the positive IgM on immunodiffusion testing, which reflects recent or acute infection [12]. The absence of central necrosis on EBUS-guided biopsy was a key morphological clue pointing away from malignancy and toward a non-necrotizing granulomatous infection, narrowing the differential to coccidioidomycosis, histoplasmosis, and sarcoidosis, among others [7]. Positive fungal cultures from BAL and IgM serology confirmed the diagnosis.

Table 1. Summary of granulomatous diseases mimicking metastatic cancer in patients with known malignancy.

Author (Year)	Primary Malignancy	Infectious Etiology	Imaging Findings Mimicking Metastasis	Method of Diagnosis	Clinical Impact
Present case	T1a GEJ adenocarcinoma	*Coccidioides* lymphadenitis	FDG-avid mediastinal lymph nodes	EBUS-FNA: granulomatous inflammation; IgM+	Avoided upstaging; curative endoscopic management preserved
Nassif *et al.* (2021)[14]	Well-differentiated liposarcoma	Disseminated coccidioidomycosis (post-COVID)	Pulmonary nodules, chest wall mass, bone lesions on CT/PET	Biopsy: granulomatous fungal infection; serology+	Avoided systemic cancer therapy; treated with fluconazole
Saenz-Ibarra *et al.* (2018) [15]	Suspected metastatic lung cancer	Disseminated coccidioidomycosis	Bilateral pulmonary nodules + extensive mediastinal/hilar lymphadenopathy on CT	Skin biopsy: spherules with endospores (PAS+)	Antifungal therapy; complete resolution of lung nodules
Stieglitz *et al.* (2014)[16]	Ewing sarcoma	Pulmonary coccidioidomycosis	18 pulmonary lesions on staging CT; 2 growing on PET after chemotherapy	Surgical resection: fungal culture grew *C. immitis*	Avoided escalation for presumed refractory metastatic disease
Smith *et al.*(1994)[17]	Suspected breast malignancy	Coccidioidal lymphadenitis	Abnormal mammogram + lymphadenopathy suggestive of malignancy	Lymph node biopsy: *Coccidioides*	Avoided cancer-directed therapy
Takanami *et al.* (2008)[18]	Esophageal cancer (2 cases)	Sarcoidosis	Intense FDG uptake in mediastinal/ bilateral hilar lymph nodes	Resected lymph nodes: noncaseating granulomas, no malignancy	Correct staging; curative resection performed
Perko *et al.*(2010)[19]	Ewing sarcoma; Hodgkin lymphoma (2 cases)	Histoplasmosis	FDG-PET findings interpreted as metastatic recurrence	Biopsy: fungal elements consistent with histoplasmosis	Avoided unnecessary chemotherapy escalation
Mackie Pohlen (2005)[20]	Metastatic melanoma	Mediastinal histoplasmosis	Extensive mediastinal/cervical nodal enlargement on PET/CT	Transbronchial biopsy + BAL: histoplasmosis	Antifungal treatment; imaging resolution
Zhang *et al.* (2022)[21]	Suspected T-cell lymphoma	Disseminated cryptococcosis	Multiple hypermetabolic lymph nodes (supra/infradiaphragmatic) + skin nodules on PET/CT	Inguinal lymph node biopsy + blood culture: *Cryptococcus*	Antifungal therapy; complete resolution on follow-up PET

Mediastinal or hilar lymphadenopathy is a well-recognized radiographic manifestation of pulmonary coccidioidomycosis and typically represents a benign reactive process. Residual pulmonary nodules, often seen on follow-up imaging, commonly represent healed infection and do not require further workup in the appropriate clinical context [12]. The Infectious Diseases Society of America (IDSA) guidelines note that antifungal treatment is not routinely required for uncomplicated coccidioidomycosis in immunocompetent individuals; however, in our patient, treatment was initiated given the ongoing surveillance needs of his GEJ malignancy, persistent lymphadenopathy of uncertain etiology would have significantly confounded oncological follow-up [13].

To contextualize the rarity and clinical relevance of our case, we conducted a review of published reports in which coccidioidomycosis, or other granulomatous infections mimicked metastatic disease in patients with known or suspected malignancy (Table 1) [14-21]. To our knowledge, this is the first reported case of coccidioidal lymphadenitis mimicking metastatic disease specifically in the setting of early-stage GEJ adenocarcinoma.

Venous thromboembolism in early GEJ cancer

The incidental finding of a subsegmental pulmonary embolism added further diagnostic complexity and initially reinforced the concern for metastatic disease, as VTE is well established as a marker of advanced cancer-associated hypercoagulability [22]. However, the rates of VTE in early-stage GEJ adenocarcinoma are not precisely defined in the literature, as most available data aggregate esophageal, GEJ, and gastric cancers and often include both early and advanced stages [23]. In population-based cohorts of patients undergoing surgery for GEJ cancer, the overall incidence of VTE within 6 months of surgery is approximately 2-4% in those not receiving chemotherapy, and up to 10% in those receiving perioperative chemotherapy [24]. In the context of our patient's clinical picture, the VTE was interpreted as an incidental finding rather than a marker of disseminated malignancy, a conclusion supported by the subsequent resolution of all abnormalities following antifungal therapy and anticoagulation.

Considerations of PET CT in neoplasia workup

The clinical consequences of false-positive PET findings in early-stage esophageal cancer are particularly detrimental.

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Cuellar et al. demonstrated a 100% false-positive rate for nodal staging by FDG-PET/CT in cTis/cT1N0 esophageal adenocarcinoma, concluding that PET/CT can be detrimental to patient management in this population [25]. Van Westreenen et al. found that 15% of esophageal cancer patients had false-positive PET lesions, and pathologic confirmation allowed 5 patients initially upstaged to M1 to undergo curative resection [26]. In a meta-analysis of 70 studies published by Deppen et al. the specificity of FDG-PET/CT drops from 75% to 61% in coccidioidal endemic regions, with granulomas accounting for 45-75% of benign diagnoses [27]. These data underscore that in our patient, failure to pursue histopathologic confirmation could have led to inappropriate upstaging from T1aN0M0 to metastatic disease, precluding curative endoscopic management and potentially subjecting the patient to unnecessary systemic chemotherapy or surgical upstaging.

Take-home message

When lymphadenopathy is discordant with the low metastatic risk of early-stage GEJ adenocarcinoma, tissue sampling is essential before any change in staging or treatment. Endemic fungal infections, particularly coccidioidomycosis, should be included in the differential diagnosis of FDG-avid lymph nodes in patients with relevant epidemiological exposure.

In conclusion, this case demonstrates that FDG-avid mediastinal lymphadenopathy in a patient with early-stage GEJ adenocarcinoma should not be presumed metastatic without histological confirmation. Coccidioidal lymphadenitis is a rare but clinically significant mimic of nodal metastasis, capable of triggering inappropriate upstaging and treatment escalation. Accurate histological diagnosis allowed our patient to avoid unnecessary systemic chemotherapy or surgical upstaging, preserving his eligibility for endoscopic surveillance and curative management. Clinicians must maintain a broad differential, including infectious etiologies, when confronted with lymphadenopathy discordant with the primary tumor stage and must recognize when to biopsy rather than presume.

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