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Paracoccidiodomycosis lung reactivation in a patient with signet-ring cell gastric adenocarcinoma after chemotherapy: Case report

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ABSTRACT

Although the relationship between paracoccidioidomycosis (PCM) and solid tumors has been described more than 80 years ago, reports of PCM and gastric cancer are rare. PCM can present before or concomitantly with the diagnosis of cancer, and its clinical presentation may rise the suspicion of malignancies or be part of reactivation by immunosuppression. We present the case of a 52-year-old Peruvian man with a signet-ring cell (SRC) gastric adenocarcinoma who after 6 chemotherapy sessions with FLOT (docetaxel, oxaliplatin, leucovorin, 5-fluorouracil) presented rapidly growing lung nodules. The lung biopsy showed yeasts compatible with *Paracoccidioides* sp., so he received initial treatment with itraconazole and after gastrectomy maintenance therapy with trimethoprim/sulfamethoxazole accompanied by tomographic resolution of lesions.
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Introduction

Paracoccidiodomycosis (PCM) is a deep endemic mycosis in tropical and subtropical zones from Latin America caused by *P. brasiliensis* and *P. lutzii*, dimorphic fungi growing saprophytically in the soil of areas with high rainfall subject to flooding, mild temperatures and presence of rivers and forest [1]. *Paracoccidioides* spp. accidentally infect human through conidia inhalation and depending of host immune response, infection can be controlled (granuloma formation) or progress to an acute/subacute or chronic disease [2]. Inside these granulomas, dormant forms of the fungus may still exist and be able to reactivate several years later under situations of disruption of the fungus-host equilibrium, developing clinical disease [3].

Brazil reports 80 % of cases of PCM in Latin America with annual incidence rates as high as 40 cases/100 000 habitants [4]. Although endemic also in Peru, its magnitude is not defined because it is not a reportable disease and available data comes mainly from local case series. Main risk factor identified in Peru are history of residence or travel to a rural area of amazon rainforest, employment as agricultural worker and male gender [5].

We describe a case of a Peruvian man with lung reactivation of PCM after receiving chemotherapy for gastric carcinoma and successful tomographic resolution after antifungal treatment.

Case report

A 52-year-old male with diagnosis of a poorly differentiated gastric adenocarcinoma with presence of signet-ring cells (SRC) with extensive perigastric, mesenteric and retroperitoneal lymph-adenopathies (clinic stage IV, T4b N3a M1) received six sessions of chemotherapy with docetaxel, oxaliplatin, leucovorin and 5-fluorouracil (FLOT) since October 2018 to January 2019.

Computed tomography was ordered in February 2019 showing diminution of lymph node size around 60 %, and appearance of new, rapidly growing lung nodules in the right middle and lower lobes (Fig. 1A–B). No respiratory symptoms, fever or further weight loss were present.

Computed tomography-guided transthoracic needle biopsy of pulmonary nodules was performed and histopathology revealed a chronic granulomatous inflammatory infiltrate with Langhans giant cells and presence of multibudding yeast cell in periodic acid–Schiff (PAS) stain, compatible with *Paracoccidioides* sp. (Fig. 2). Immunodiffusion test for *Histoplasma* spp. and *Paracoccidioides* spp. were negative. Cryptococcal antigen (CrAg) in serum was negative. The fungal cultures of the biopsy specimen were negative. Erythrocyte sedimentation rate (ESR) was 113 mm/h.

It was found that the patient had lived in Pucallpa approximately 35 years before (low jungle of Peru) in his youth.

Treatment was started with itraconazole 200 mg QID for 4 months with an improvement of ESR (12 mm/h) and tomographic resolution of lung lesions (Fig. 1C). A total gastrectomy with D2

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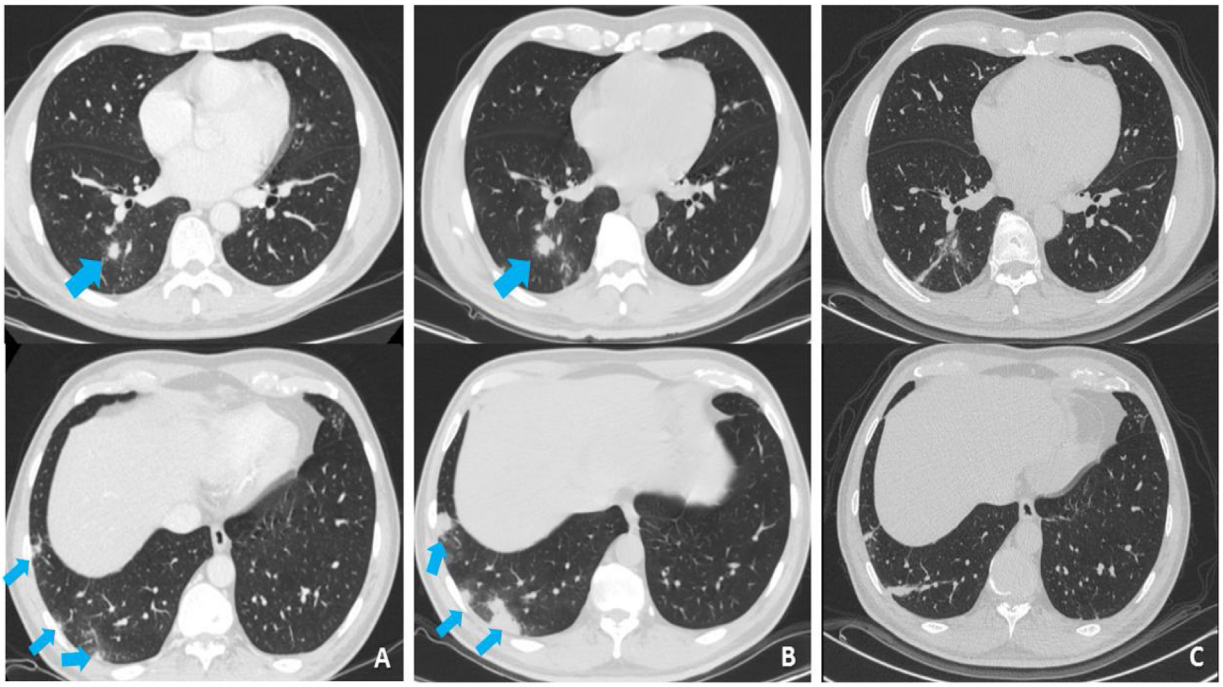

Fig. 1. Non-contrast chest CT: (A) Appearance of fast-growing nodules in the right lung parenchyma at the end of the first course of chemotherapy with FLOT. (B) Control CT one week later. (C) Residual scarring lesions, after 4 months of antifungal treatment.

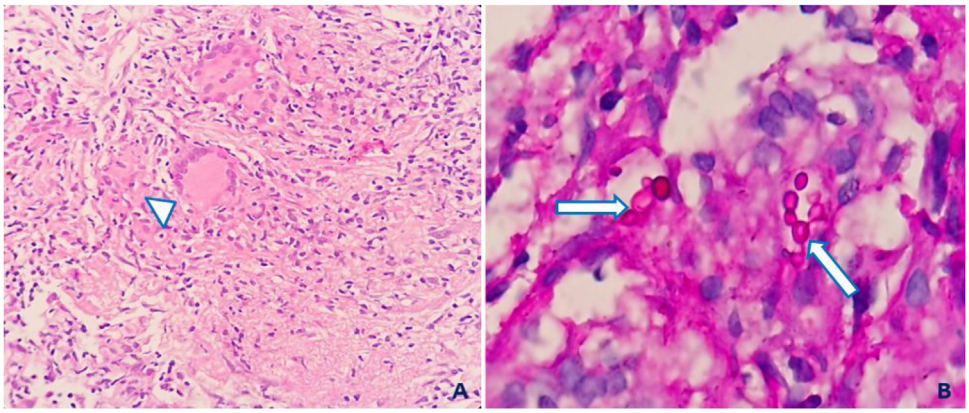

Fig. 2. Lung biopsy: (A) Chronic granulomatous inflammation with the presence of Langhans giant cells (arrowhead). H&E stain, 40 × . (B) Presence of budding yeasts compatible with *Paracoccidioides* spp. (arrows). Periodic acid–Schiff (PAS) stain, 100 × .

lymphadenectomy was performed (June 2019). The biopsies performed showed a single lymph node group positive to neoplasm. No fungal involvement in lymph nodes or stomach was observed. During the perioperative period he received treatment with amphotericin B deoxycholate and at discharge antifungal maintenance with trimethoprim/sulfamethoxazole (TMP-SMX 160/800 mg BID) for additional 8 months. Tolerance to therapy was good. No evidence of reactivation of fungal infection occurred. The patient was treated with radiotherapy and chemotherapy with capecitabine during this period. However, developed bone metastases, confirmed by histopathology, with clinical deterioration causing finally his death.

Discussion

PCM information in immunocompromised host is limited even though their association has been described since 1933 [6]. Patients with solid tumors usually develop the chronic form of the disease, most of which are epidermoid carcinoma of the digestive and respiratory tract. We found fewer than 10 reported cases of association between PCM and gastric cancer, most of them epidermoid and other unspecified [3,7]. Our case constitutes an association between gastric adenocarcinoma with SRC and PCM, not reported previously in the literature.

It appears that cancer does not affect the natural history of PCM and data timing of diagnosis indicate that it may occur before, concomitantly or after cancer diagnosis in the case of solid tumors [3,7]. The chronic form of PCM in this case had as risk factors the advanced stage of gastric adenocarcinoma and presumably chemotherapy-associated immunosuppression with FLOT, leading to the reactivation of lung quiescent foci probably acquired during his stay in an endemic area.

When the immune response is successful, the infection is blocked at the level of PCM primary complex (pneumonitis, ascending lymphangitis and satellite lymph node affectation), producing scar formation that can be sterile or contain viable organisms in a latency state for several years [7]. The disruption of the fungus-host equilibrium by immunosuppression states (HIV/

AIDS infection, malignancies, chemotherapies, immunotherapies, organ transplantation and congenital immunological failures) can lead to reactivation of latent foci and disease progression [2,3].

The diagnosis of PCM is difficult in immunocompromised hosts. Availability to us of nucleic acid-based assays or gp43KDa antigen detection is limited. The diagnosis in these scenario is based on the histopathological examination in which parent cell with multiple attached buds by narrow connections, the pathognomonic "ship's wheel" budding yeast cells, can be seen [8].

This case was assessed as mild chronic PCM because there was only evidence of one organ involvement and weight loss was less than 5%. The Brazilian consensus for clinical management of paracoccidioidomycosis does not propose a recommendation in cancer [9]. We started with itraconazole until gastrectomy, followed by amphotericin B perioperatively, and finally several months of TMP/SMX with good response.

There is evidence that itraconazole therapy is superior to TMP-SMX in terms of clinical, radiological and immunological cure (86.4 % vs 51.3 %) and with a median treatment period significantly shorter (12 vs 23 months) [10].

Efficacy and effectiveness of complementary treatment with itraconazole followed by TMP-SMX regimen were similar to itraconazole and TMP-SMX monotherapy, however the time to serological cure (persistently negative results for specific antibodies for more than one year) in the sequential therapy group was greater than the other groups [11]. The duration of antifungal treatment in immunosuppression is not defined, and depends on clinical response, laboratory and imaging monitoring, and improvement of immunosuppression. Immunodiffusion test was not used for follow-up because of negative initial result.

The usefulness of serological tests in the diagnosis of PCM in immunocompromised hosts with solid tumors is approximately 50 % [12] and it can be used to evaluate therapeutic response. In our case, ESR was between normal values to the fourth month of therapy. We also consider and propose other tools for follow-up such as positron emission tomography [13].

PCM mortality is apparently higher in patients with HIV or lymphomas than solid tumors. In cancer patients with PCM, mortality may be more strongly associated to toxicity secondary to chemotherapy or advanced cancer stage [3,7,12]. Despite the favorable evolution of fungal disease in the present case, the progression of neoplasm was inevitable due to the aggressiveness of histologic subtype, subsequently generating metastasis leading to a fatal outcome in the patient. A differentiation of PCM progression for gastric adenocarcinoma subtypes could be proposed.

Conclusion

The reactivation of PCM in the context of a gastric adenocarcinoma with signet-ring cell is an unusual presentation. PCM should be included in the differential diagnosis of pulmonary nodules in any oncological patient from endemic areas.

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Declaration of Competing Interest

The authors declare no conflicts of interest for this article

CRediT authorship contribution statement

F. Soto-Febres: Investigation, Writing - original draft, Writing - review & editing. **A. Morales-Moreno:** Writing - original draft, Data curation. **J. Arenas:** Writing - original draft, Data curation. **G. Pérez-Lazo:** Investigation, Supervision.

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