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BRIEF REPORT

Isolated Pulmonary Emergomycosis in an Immunocompetent Patient in Alberta, Canada

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Emergomyces canadensis pulmonary infection was incidentally diagnosed in an asymptomatic patient suspected to have metastatic osteosarcoma. Molecular diagnosis was imperative to fungal identification given overlapping histopathological features with histoplasmosis. This report documents a case of isolated pulmonary emergomycosis in an otherwise immunocompetent patient while discussing diagnostic and management pitfalls of this emerging and underdiagnosed infection.

Keywords. *Emergomyces*; granuloma; *Histoplasma*; thermally dimorphic.

Emergomyces are thermally dimorphic fungi implicated in emergomycosis, an infection almost exclusively affecting immunocompromised hosts [1]. Previously classified among the genus *Emmonsia*, *Emergomyces* differ in their ability to undergo a temperature-dependent conversion into a yeast phase in the host [2]. Both *Emergomyces* and *Emmonsia* belong to the family *Ajellomycetaceae*, which includes the thermally dimorphic fungi *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis* [2].

We report the first case of localized pulmonary asymptomatic infection due to *Emergomyces canadensis*. The infection clinically mimicked metastatic disease in an otherwise immunocompetent osteosarcoma patient and mimicked *Histoplasma capsulatum* infection on histopathology. This case illustrates a new clinical presentation of emergomycosis, contributing to the understanding of the disease spectrum associated with this fungal species that has thus far only been identified in North American patients.

CASE REPORT

The patient was a 17-year-old male from Alberta, Canada, diagnosed with localized osteosarcoma of the left lower femur. The malignancy was treated with neoadjuvant chemotherapy (cisplatin, methotrexate, and doxorubicin) followed by gross total resection and total knee replacement, plus postoperative adjuvant chemotherapy for a total of 29 weeks of chemotherapy.

Approximately 1 year after completion of chemotherapy, a chest computed tomography (CT) scan revealed a single nodular density measuring 5 mm in diameter in the anteromedial segment of the left lower lobe, surrounded by ground glass haziness (Figure 1). The finding was new in comparison with imaging obtained ~3 months earlier. An abdominal ultrasound was negative for hepatic and splenic lesions, and a nuclear medicine scan was negative for bony lesions. Metastatic osteosarcoma in the form of a single lung nodule was suspected and subsequently completely resected.

Histopathological examination of the lung nodule did not reveal malignancy, but rather unexpectedly showed a necrotizing granuloma surrounded by organizing pneumonia (Figure 2). Grocott's methenamine silver (GMS) stain identified round, yeast-like organisms 2–4 μm in size with single narrow-based budding. No hyphae or pseudohyphae were identified. The organisms were poorly visualized with hematoxylin & eosin and were only faintly positive on periodic acid Schiff (PAS) staining. Mucicarmine, Fontana Masson, and Ziehl-Neelsen stains were negative. In the context of the histopathological findings, infection due to *Histoplasma capsulatum* or *Emergomyces canadensis* was favored.

Follow-up assessment revealed a history of travel preceding the diagnosis of cancer to a *Histoplasma*-endemic area in Canada (Québec), as well as to the United States (California, Nevada, Florida, Washington DC, and Oregon), Germany, France, Italy, and Romania. There was no new travel during or after completion of chemotherapy.

Postsurgery *Histoplasma* serum immunodiffusion (IMMY, Norman, OK, USA) and serum and urine antigen (Mira Vista Diagnostics, Indianapolis, IN, USA) were negative. Formalin-fixed paraffin-embedded (FFPE) lung tissue was referred to the Molecular Microbiology Section at the University of Washington Department of Laboratory Medicine and Pathology (Seattle, WA, USA). Whereas the tissue was negative by *Histoplasma* nested polymerase chain reaction, nested amplification

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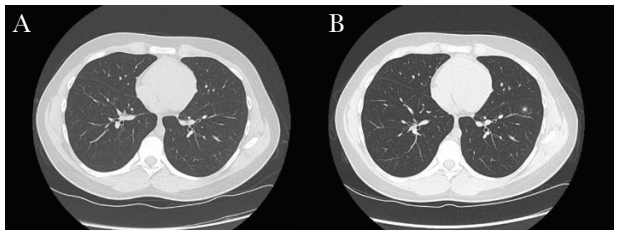

Figure 1. Radiographic comparison demonstrating a new-onset solitary lung nodule. A chest computed tomography scan demonstrated a new-onset 5-mm nodule in the anteromedial segment of the left lower lobe. A, February 2021. B, May 2021.

followed by sequencing of fungal Internal Transcribed Spacer (ITS) confirmed the presence of *Emergomyces canadensis* DNA in the sample.

In the absence of both clinical and radiological evidence of dissemination and given excision of the single known focus of infection in an otherwise immunocompetent and asymptomatic patient, the fungal infection was managed expectantly. Antifungal therapy was reserved for the event of clinical progression of infection or for preemptive use in case of future immune suppression.

DISCUSSION

Emergomyces infections have been recorded since at least the 1990s [1]. Thanks to ever-improving diagnostic capabilities and revised taxonomy, the worldwide emergence of this not-so-new group of dimorphic fungi has only recently become evident in clinical practice. This case of *Emergomyces canadensis* infection presenting as a solitary lung nodule in an otherwise immunocompetent asymptomatic cancer patient expands our current understanding.

Es. canadensis has been exclusively documented in North America, between 1992 and 2015, in patients from Canada (Saskatchewan n = 2) and from the Southwestern United States (Colorado n = 1 and New Mexico n = 1) [3]. Other species have been documented elsewhere, across Europe (*Es. europaeus*, *Es. pasteurianus*), Africa (*Es. africanus, Es. pasteurianus*), and Asia (*Es. orientalis, Es. pasteurianus*) [1]. A natural reservoir of these pathogens remains unknown [1].

Infection is presumed to occur via inhalation [1]. Detection of *Emergomyces* DNA in air samples and pulmonary involvement in the vast majority of cases—including the one reported here—supports this assumption [1]. The interval between primary infection and clinically apparent disease, corresponding to latent or subclinical infection, is currently unknown. Dissemination of infection beyond the lungs may occur, with fever, anemia, elevated liver enzymes, and weight loss frequently seen [4]. Protean skin manifestations are common in the setting of dissemination, offering an important but nonspecific diagnostic clue [5]. Dissemination to the liver, spleen, gastrointestinal tract, lymph nodes, bone marrow, and cervix have been previously described, although less frequently [3, 6]. Advanced HIV infection, therapeutic immunosuppression, and diabetes have been associated with disseminated disease at presentation

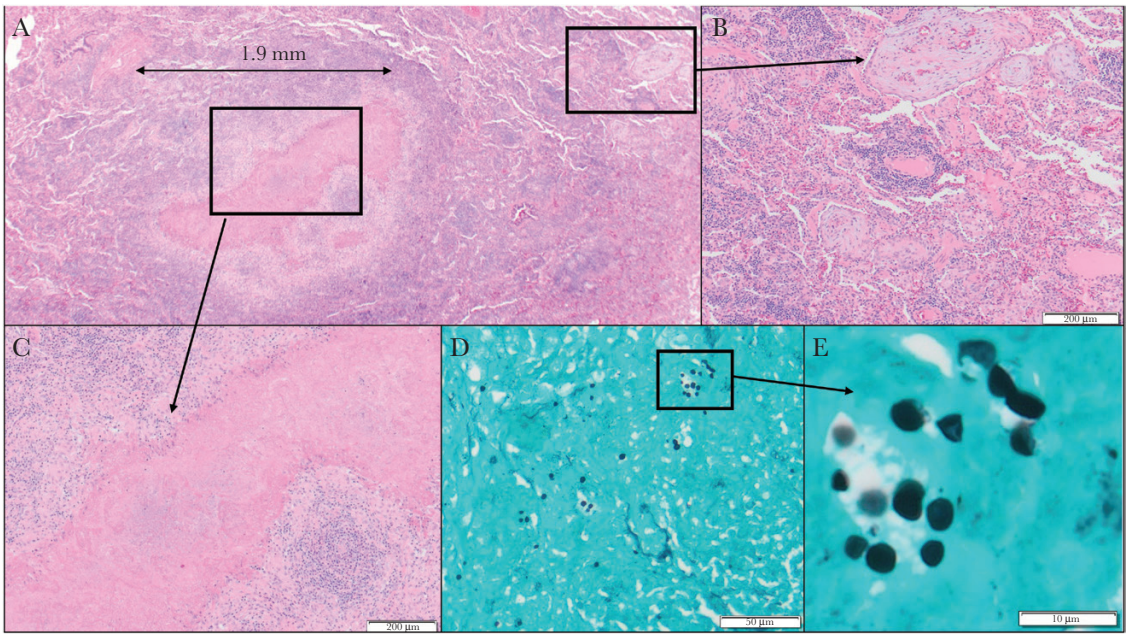

Figure 2. Granulomatous reaction to *Emergomyces canadensis* pulmonary infection. A (20×), A solitary necrotizing granuloma surrounded by interstitial lymphoplasmacytic infiltrate and organizing pneumonia with Masson bodies (B, 40×). There were areas of obliterative bronchiolitis and foam cells consistent with an endogenous localized lipoid pneumonia. The granuloma was filled with necrotic debris and surrounded by epithelioid histiocytes and multinucleated giant cells (C, 40×). On Grocott's methenamine silver stain, the organisms appeared as uniform, round, yeast-like organisms with size ranging from 2 to 4 microns (D and E, 200× and 1000×, respectively).

[3, 6–8]. Disseminated emergomycosis has rarely been documented in the absence of obvious immune-compromising conditions or therapies, and isolated yet multifocal pulmonary infection has been previously reported in the setting of immunosuppression [9]. Fungal and host determinants of progression and dissemination of the infection remain to be characterized. Asymptomatic localized infection in this case may, at least in part, reflect the immunocompetent status of the host, similar to *Histoplasma* and *Blastomyces* infections where the majority of infections in immunocompetent hosts are subclinical or self-resolving. As no screening test is currently available to ascertain exposure to *Emergomyces*, the frequency of latent, subclinical, or self-limited disease is still unknown.

A high index of suspicion is necessary for the laboratory diagnosis of emergomycosis. Shared characteristics with other *Ajellomycetaceae* preclude *Emergomyces* identification based solely on morphological features on histopathology or culture. Its yeast phase seen in human tissues and within macrophages bears striking similarities with *Histoplasma capsulatum*, with both presenting as narrow-based budding yeasts measuring 2–5 μm, while its mold phase in culture closely resembles *Blastomyces dermatitidis* [2, 5]. Definitive organism identification requires amplification and sequencing of fungal ITS DNA, as achieved in FFPE tissue in this case. Isolation of the organism is feasible on standard fungal culture media for respiratory and biopsy specimens, and in aerobic or mycobacterial/fungal lytic vials of commercial blood culture systems [6]. Additional diagnostic challenges may arise from the known cross-reactivity of commercially available assays targeting the closely related fungi *Histoplasma capsulatum* and *Blastomyces dermatitidis*. *Histoplasma* antigen testing of serum and urine may yield positive results in the setting of disseminated emergomycosis, while *Blastomyces dermatitidis* DNA probe hybridization may also be positive when performed on *Emergomyces* isolated in culture [3, 10].

In this case, both emergomycosis and histoplasmosis were suspected based on the histopathological findings and local epidemiology. Whereas the histopathology of *Emergomyces canadensis* infection has not been previously described beyond the appearance of its yeast forms, granulomatous responses similar to those seen in histoplasmosis have been previously observed in *Es. pasteurianus* and *Es. orientalis* regardless of their presentation as localized or disseminated infections, respectively [3, 7, 11]. Autochthonous cases of both infections have been previously reported in the Canadian prairies. Recent local acquisition of infection was favored given the documentation of a new isolated pulmonary nodule long after expected achievement of immune reconstitution postchemotherapy. However, reactivation of latent infection remotely acquired, locally or elsewhere, is also plausible as chemotherapy and/or other stressors could have contributed to insidious progression of disease until its dimensions eventually allowed for detection by chest CT scan.

Connecting the histopathology and imaging in this case, the ground glass associated with the pulmonary nodule seen on chest CT correlated with the organizing pneumonia as seen on histopathology. The halo sign, ground glass attenuation surrounding a pulmonary nodule, is a nonspecific CT finding that can be seen in association with malignancies and other granulomatous infections [12]. A wide range of imaging abnormalities have been described in emergomycosis including diffuse reticulonodular disease, focal consolidation, lobar atelectasis, effusions, and adenopathy, but no unique distinguishing radiological feature has been described to date [6].

Case fatality in disseminated emergomycosis has been estimated to be as high as 48% [6]. Early recognition and treatment are key, whereas fungal isolation from blood may be a terminal indicator [4]. In the absence of randomized controlled trials, the recommended treatment of disseminated emergomycosis consists of amphotericin B for 10–14 days, followed by prolonged itraconazole therapy. This recommendation mirrors guidelines for management of histoplasmosis and is informed by reported patient outcomes [6]. Observations are concordant with available antifungal susceptibility data, with minimal inhibitory concentrations being highest for echinocandins and fluconazole, and lowest for amphotericin B, itraconazole, voriconazole, posaconazole, and isavuconazole [3–5]. Recommendations for management of localized infections such as the one reported here are still lacking. Expectant management of localized infection in otherwise immunocompetent patients could be considered in this context.

In summary, we report a case of incidentally identified localized emergomycosis in an immunocompetent host and the fifth documented case of infection due to *Emergomyces canadensis*. These findings suggest that *Emergomyces* may cause asymptomatic pulmonary infection in immunocompetent hosts and further expand the spectrum of disease it causes. Due to laboratory test cross-reactivity and morphological similarities with *Histoplasma capsulatum* and *Blastomyces dermatitidis*, *Emergomyces* may be frequently misidentified, with the laboratory diagnosis of emergomycosis relying on confirmatory fungal DNA sequencing. Closing knowledge gaps in the clinical management of this infection requires increased clinical suspicion and pursuit of confirmatory testing, particularly when histoplasmosis or blastomycosis is suspected.

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Patient consent. Parental written consent was obtained. Research ethics board review was not required by the University of Calgary Conjoint Health Research Ethics Board as per their interpretation of the second edition of the Government of Canada Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2).

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