

# Erythema nodosum as key manifestation of histoplasmosis case

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Accepted 4 November 2022

## SUMMARY

Histoplasmosis is a systemic infection caused by the fungus, *Histoplasma capsulatum*. Infection of *H. capsulatum* frequently occurs by inhaling the spores of the fungus, which is found in bat and bird droppings, or soil enriched with their excrement. If not detected and treated, histoplasmosis can develop late, severe complications such as mediastinal fibrosis, or even develop into a disseminated infection. However, histoplasmosis infections are often asymptomatic, making its detection more difficult. Further, only 6% of histoplasmosis cases will present with erythema nodosum, with most cases associated with female patients. This case presents a woman in her 50s with a pertinent history of fibromyalgia and hypothyroidism secondary to Hashimoto's who initially sought medical care for painful nodules on her legs and was eventually diagnosed with histoplasmosis. This report clearly demonstrates the importance of maintaining a broad differential when working up inflammatory manifestations, such as erythema nodosum.

## BACKGROUND

Histoplasmosis is a systemic infection caused by inhalation of the spores of the fungus *Histoplasma capsulatum*. Histoplasmosis is the most common endemic mycosis in the USA and is especially prevalent in river valley areas of the USA, such as Ohio and Mississippi.<sup>1</sup> *H. capsulatum* flourishes in moist soil and is found in bat and bird droppings.<sup>2</sup> Infection with *H. capsulatum* is often clinically silent. Symptomatic histoplasmosis is associated with nonspecific symptoms, such as cough and fever, and thus is often unrecognised, misdiagnosed and mistreated.<sup>3</sup> However, early diagnosis and treatment is key, as histoplasmosis can become disseminated or develop complications such as mediastinal fibrosis.<sup>1</sup>

Erythema nodosum is a common nodular septal panniculitis characterised by sudden onset of painful firm, erythematous nodules, mainly concentrated on the anterior surface of the legs. It is a reactive process that may be triggered by a broad variety of stimuli, including infections, inflammatory bowel disease, autoimmune disorders and medications.<sup>4</sup> Only 6% of histoplasmosis cases will develop erythema nodosum and it is more commonly seen with female patients.<sup>2</sup>

## CASE PRESENTATION

A woman in her 50s with a medical history significant for fibromyalgia and hypothyroidism secondary to Hashimoto's presented for an evaluation of

painful nodules on her legs and knees. She developed bumps around her knees and shins over the past week. The bumps started off as bright red and slowly became more bruise-like. The patient also noticed that her legs were much more swollen than usual. She reported that her fibromyalgia symptoms had been worse in recent weeks with an increase in myalgia and lethargy.

Recently, the patient had pharyngitis of unknown aetiology 3 weeks prior and visited Central America 6 weeks prior to this visit. She was also in the process of being worked up for chronic left upper quadrant pain and endorsed an increase in constipation and dark stools for previous 10 days.

On physical examination, the patient appeared well nourished, awake, alert, oriented and in no apparent acute distress. Integument examination showed multiple raised tender nodules present on both shins and knees. Some nodules appeared bright red while others appeared similar to old bruising. The nodules were tender to the touch. The rest of the physical examination was unremarkable.

The patient medications included amitriptyline hydrochloride, levothyroxine sodium, naltrexone hydrochloride, and topiramate.

## INVESTIGATIONS

The skin lesions ([figure 1](#)) were very typical for erythema nodosum. As mentioned in the background section, erythema nodosum is often observed as sequelae of reactive processes, such as infections, inflammatory bowel disease, autoimmune disorders and HIV. Due to the variety of stimuli that can trigger erythema nodosum, initial differential was broad and focused on autoimmune and infectious causes.

The patient does have a history of autoimmune disorder (chronic lymphocytic thyroiditis, also known as Hashimoto's disease). She also has a positive family history of multiple family members with systemic lupus erythematosus. In addition, she has had chronic left upper quadrant pain and recent constipation, which could indicate inflammatory bowel disease. However, she has no known family history of inflammatory bowel disease and has never had a colonoscopy. Such autoimmune conditions can precipitate erythema nodosum through mechanisms involving a type IV delayed hypersensitivity reaction in response to the increased levels of antigens observed with autoimmune disorders (4). To cover potential autoimmune causes, laboratory tests were ordered for the following: Thyroid-stimulating hormone, C reactive protein (CRP), antinuclear antibody (ANA) screen, HIV antibody



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**To cite:** Wang S, Morrical J. *BMJ Case Rep* 2022;**15**:e251876. doi:10.1136/bcr-2022-251876



**Figure 1** Erythematous nodules on patient's legs consistent with erythema nodosum.

and antigen, anti neutrophil cytoplasmic antibody level (ANCA), cyclic citrullinated peptide antibody IgG, and rheumatoid factor IgM. A referral was scheduled for a colonoscopy.

The patient travelled to Central America 3 weeks prior to this visit and had a severe gastrointestinal illness with nausea, vomiting, diarrhoea, fever and chills. The patient had an unspecified influenza-like illness 3 weeks prior to this visit that was negative for COVID-19. To cover potential underlying infectious causes, anti-streptolysin O (ASO), tuberculosis (TB) blood test and chest X-rays were ordered.

The patient's testing revealed inflammation with elevated CRP levels. ANA, HIV, ANCA, ASO and TB screens came back negative. IgG and IgM levels were within normal limits. However, her chest x-ray revealed prominence in the left lung hilum. A follow-up CT scan was ordered for further investigation and the patient was referred to a pulmonologist.

Initial CT scan revealed an 8mm nodule in the left lower with mediastinal and left hilar lymphadenopathy. The radiologist expressed concerns for bronchogenic carcinoma and recommended tissue diagnosis and/or positron emission tomography scan. However, the pulmonologist suspected an infectious process as opposed to malignancy since there were no nodules in her previous CT scan 4 months prior. Pulmonology wanted to first obtain labs prior to a biopsy. Given an associated halo sign on X-ray, the pulmonologist recommended screening for fungal infections including histoplasmosis, blastomycosis, cryptococcus, coccidioidomycosis, aspergillosis.

Serum histoplasmosis markers were positive. This and her constellation of symptoms including halo sign on X-ray and erythema nodosum made the diagnosis of histoplasmosis likely.

## TREATMENT

Initially, the patient was given diclofenac sodium 75mg delayed release tablet twice daily, lidocaine-prilocaine cream for topical anaesthesia as needed, and non-steroidal anti-inflammatory drug therapy for symptom management. After testing positive for histoplasmosis, the patient was started on itraconazole 200mg once a day. Ten days into treatment, blood testing demonstrated that her serum levels of itraconazole were low, and she was increased to 200mg two times per day.

## OUTCOME AND FOLLOW-UP

Initial histoplasma antibody testing with complement fixation titres of histoplasma mycelial were 1:128, with complement fixation titres >1:32 associated with active disease.<sup>2</sup> Three weeks later, after therapeutic treatment, histoplasma mycelial levels dropped to 1:64. The erythema nodosum resolved within 1 week of starting the

itraconazole. The patient is being referred to an infectious disease specialist for continuation of care.

The patient later discovered that there was a dead bird in the ceiling tiles above her desk when rewiring work was being done. She shared that she works in a building with high rafters where birds are commonly found. The patient was educated that bird droppings are a common vector for histoplasmosis. She has since moved from her current desk to a desk a few feet away and is working on obtaining accommodations for her work environment.

## DISCUSSION

This case supports existing literature on the route of infection for histoplasmosis, despite presenting with a unique initial manifestation. Histoplasmosis (*H. capsulatum*) is a common pulmonary disease of fungal origin. In endemic areas of the USA, it is estimated that 60%–90% have been infected with *H. capsulatum* at least once in their lifetime.<sup>3</sup> However, many cases of histoplasmosis are asymptomatic. Even when symptoms persist, they are often nonspecific, such as myalgia, arthralgia, fever and cough.<sup>2</sup>

Erythema nodosum is the most common type of panniculitis and is characterised by painful, erythematous subcutaneous nodules on the pretibial surface of the lower extremities. It is the result of an inflammatory process that involves the septa between subcutaneous fat lobules and likely involves a type IV delayed hypersensitivity response.<sup>5</sup> Although streptococcal pharyngitis is the most common cause of erythema nodosum,<sup>5</sup> it can also be the first sign of other systemic complications like bacterial or fungal infections, autoimmune diseases, cancer or drug interactions.

Erythema nodosum is a rarer manifestation of histoplasmosis and only occurs in approximately 6% of cases.<sup>2</sup> One of the first case reports of erythema nodosum with histoplasmosis was featured in the Journal of the American Medical Association (JAMA) in 1959, which noted that 'although erythema nodosum is not an uncommon manifestation of a deep fungal infection, such as coccidioidomycosis, to our knowledge there have been no reported association of this syndrome with histoplasmosis.'<sup>6</sup> Another study published in JAMA in 1981 found that 4% of histoplasmosis patients were initially seen with erythema nodosum (11 of 431 cases), where 9 of the 11 patients were female.<sup>7</sup> The diagnostic workup discussed in this patient's case of erythema nodosum follows current literature guidelines, including CRP level, streptococcal infection and TB testing.<sup>5</sup> In addition to laboratory-based testing, chest X-rays are also an appropriate step in the workup of erythema nodosum, as pulmonary infections such as TB or fungal diseases can have distinctive pulmonary X-ray findings and are associated with erythema nodosum. The 'halo sign' refers to ground glass attenuation around a lung nodule and is a nonspecific sign of infectious diseases, including fungal infections.<sup>8</sup> Micronodules with a random pattern of dissemination and airspace consolidations are other tomographic findings associated with histoplasmosis.<sup>8</sup> In this patient's case, the results of diagnostic laboratory testing coupled with positive lung findings on imaging prompted further testing of specific fungal infections, including histoplasmosis.

Gold standard of diagnosing histoplasmosis is to isolate *H. capsulatum* on culture media. However, this is a lengthy process that can take several weeks and is less sensitive in acute and subacute levels of infection.<sup>1</sup> Given these difficulties, serology tests can provide faster information with 70%–100% specificity and 70%–90% sensitivity.<sup>1</sup> In this patient's case, the positive results of the complement fixation blood tests, the imaging results, and the clinical data were enough to make a diagnosis of histoplasmosis highly suspect.

It is prudent to note that sarcoidosis is an inflammatory process associated with similar patient presentations to this case, including

erythema nodosum and fatigue. Sarcoidosis can also be associated with increased serum inflammatory markers and ground glass opacities on CT. However, sarcoidosis is commonly associated with bilateral hilar lymphadenopathy, whereas our patient case had left-sided findings only.<sup>9</sup> The gold standard for diagnosis of sarcoidosis is biopsy. However, given the positive histoplasmosis titres and imaging findings that strongly supported a diagnosis of histoplasmosis, a biopsy procedure for sarcoidosis was not pursued.

The association between histoplasmosis and bat and bird droppings has been well demonstrated and supported by this case. A study that investigated nearly 3000 histoplasmosis cases in the USA between 1938 and 2013 found that 77% of outbreak settings involved birds, bats or their droppings.<sup>9</sup> Two common animal vectors of *H. capsulatum* are bats, who carry the fungus in their gastrointestinal tract, and birds, who carry the fungus on their feathers.<sup>2</sup> The aforementioned study also found that 41% of exposures were due to the workplace environment.<sup>10</sup> Workplace environment was not an obvious initial factor in our patient's case, as she works a desk job in an indoor facility. However, shortly after diagnosis, rewiring work was being done in the ceiling above her desk and a dead bird was discovered. The patient then shared that the building she works at has high rafters where birds are commonly found. With her workplace exposure and supporting literature, it is highly suspect that bird droppings may have been the source of *H. capsulatum* in her case.

A literature search for erythema nodosum in histoplasmosis cases reveals a gap in literature in the last ten years. Larger studies that

investigate the relationship between this fungal infection and this inflammatory skin condition are largely outdated.<sup>7,10</sup> These studies do, however, note the rare but strong association of erythema nodosum with histoplasmosis infections, overwhelmingly with female patients. As a result, case presentations such as the one discussed serve as an important reminder to include fungal infections as a differential diagnosis in the workup of erythema nodosum, especially if the patient is female.

**Acknowledgements** I wish to thank to JM for her continued support and thank all the staff at Holland Community Health Center/Holland Hospital for their care. I also thank MT at Michigan State University College of Human Medicine for his work as student research director.

**Contributors** SW, Michigan State University College of Human Medicine, made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of the work; drafting the work and critically revising the work. JM, Holland Hospital, served as scientific advisor, critically reviewed the study proposal, and gave final approval of the version of this study to be published.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Consent obtained directly from patient(s).

**Provenance and peer review** Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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#### Learning points

- ▶ Infection with histoplasmosis is often asymptomatic and should be included in the differential workup of diagnosing inflammatory complaints.
- ▶ Underlying fungal infections should be considered in erythema nodosum, especially in female patients.
- ▶ Sarcoidosis can present similarly to histoplasmosis but is more commonly associated with bilateral hilar lymphadenopathy. Thorough workup should be completed prior to biopsy.
- ▶ Aggregation of complement fixation tests, diagnostic findings and clinical data can be a valid alternative to time-consuming culture techniques in diagnosing histoplasmosis.
- ▶ Review all diagnostic findings with the consideration of other clinical data gathered by the physician to avoid mistreatment/misdiagnosis.

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