A SELF-TEST ON A CLINICAL CASE

CME CREDIT

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A young man with a cough, an abnormal chest radiograph, and multiple skin lesions

A PREVIOUSLY HEALTHY 23-year-old man is referred because of a persistent cough, skin lesions, and an abnormal chest radiograph.

The cough, which began about a month ago, initially produced a small amount of yellowish sputum. The patient's primary care physician gave him a course of oral penicillin, but he did not improve.

At that point, a chest radiograph revealed an infiltrate in the lower lobe of the right lung. He was given azithromycin and improved somewhat. However, he continued to have paroxysms of coughing and developed multiple skin lesions over his face and arms. A chest radiograph 4 weeks after the initial presentation showed that the infiltrate had not resolved.

He denies any constitutional symptoms, pleuritic chest pain, bone pain, headache, or hematuria. He has not recently travelled or been exposed to pets, and he has lived in Ohio all his life. A recent purified protein derivative test was negative.

On physical examination, he is afebrile and his vital signs are normal. He has multiple hard, nontender erythematous nodular lesions over his face and left forearm (FIGURE 1). The rest of his physical examination is normal.

A complete blood cell count, chemistry panel, and liver function tests are normal. A sputum smear for mycobacteria and fungi is negative. Blood, sputum, and urine cultures are also negative.

A new chest radiograph reveals a dense consolidation in the right lower lobe (FIGURE 2).

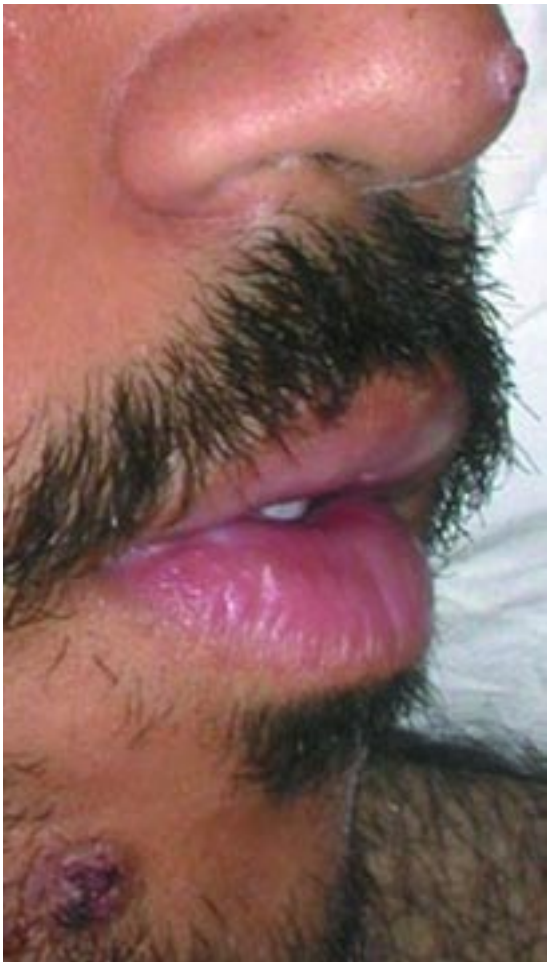

FIGURE 1. Nodular, erythematous lesions over the nose and chin.

The differential diagnosis of pulmonary infiltrates and skin lesions is extensive

A computed tomographic scan of the chest, obtained because the infiltrate has not resolved after 1 month of illness and two

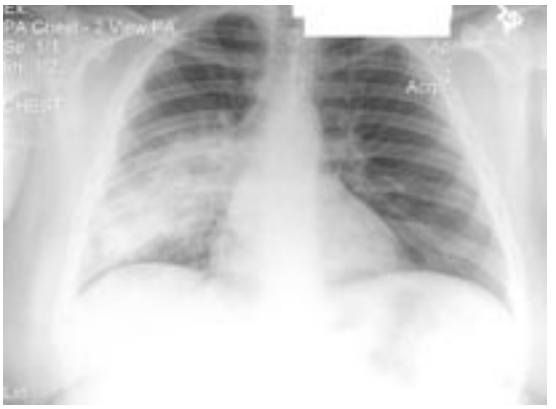

FIGURE 2. The chest radiograph shows a consolidation in the right lower lobe.

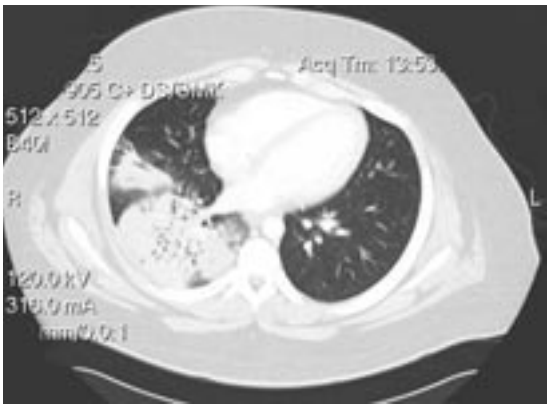

FIGURE 3. The patient's computed tomographic scan shows a consolidated density in the right infrahilar region with peripheral alveolar infiltrates.

antibiotic courses, shows a consolidated density in the right infrahilar region with peripheral alveolar infiltrates (FIGURE 3). Subcarinal lymph nodes are prominent; however, there is no significant hilar or mediastinal lymphadenopathy.

DIFFERENTIAL DIAGNOSIS

1 Which of the following should be considered in the differential diagnosis?

- ❑ Sarcoidosis
- ❑ Histoplasmosis
- ❑ Sporotrichosis
- ❑ Blastomycosis
- ❑ Lymphomatoid granulomatosis

Standard bacterial cultures will not grow *Histoplasma*

All of the above should be considered. The differential diagnosis of pulmonary infiltrates and skin lesions is extensive and includes:

- Fungal, mycobacterial, and viral infections
- Granulomatous diseases such as sarcoidosis
- Vasculitic and connective tissue diseases, including Churg-Strauss syndrome, Wegener granulomatosis, Sjögren syndrome, systemic lupus, and rheumatoid arthritis
- Neoplastic disorders such as metastatic diseases or non-Hodgkin lymphoma, including mycosis fungoides and Sézary syndrome.

Sarcoidosis

Sarcoidosis, a multisystem granulomatous disorder of unknown cause, is characterized by noncaseating granulomas in the organs involved.

The lungs are involved in 90% of cases. The typical radiographic features are bilateral hilar and mediastinal adenopathy, and parenchymal abnormalities that can be interstitial or alveolar. Consolidation and nodular opacities are seen.

The skin is involved in approximately 20% of cases. Typical dermatologic manifestations include erythema nodosum, lupus pernio, and a maculopapular eruption that involves the alae nares, lips, forehead, eyelids, and nape of the neck.

Löfgren syndrome is a combination of erythema nodosum hilar adenopathy, polyarthralgias, and fever, a constellation mostly seen in women.[1] Lupus pernio is a violaceous indurated discoloration of the nose, cheeks, chin, and ears.

Other extrapulmonary organs commonly involved are the eyes, reticuloendothelial system, musculoskeletal system, heart, exocrine glands, and central nervous system.

Histoplasmosis

Histoplasmosis and its causative organism *Histoplasma capsulatum* is found worldwide. It is the most common endemic mycosis in the United States; most cases occur in the Ohio and Mississippi river valleys. Activities and occupations most likely to result in infection involve exposure to soil, particularly soil that is enriched with bird and bat droppings (eg, in farmers, gardeners exposed to poultry manure, earth-moving operators, and landscapers).

The clinical spectrum of pulmonary histoplasmosis varies according to the extent of exposure, presence of underlying lung disease, and immune status of the patient. It can present as asymptomatic pulmonary infection, acute symptomatic pulmonary infection, disseminated histoplasmosis, chronic pneumonia, or fibrosing mediastinitis.

Skin involvement occurs in 10% to 20% of cases of disseminated histoplasmosis. The characteristic lesions include nodules, papules, plaques, ulcers, vesicles, oral ulcerations, and generalized dermatitis.

Chest radiographs in cases of acute pulmonary infection usually show enlarged hilar or mediastinal nodes with focal infiltrates.

Diagnosis requires special fungal stains, cultures, and antigen detection in serum or urine. Standard bacterial cultures of blood or tissue samples will not grow *Histoplasma*, although the organism can be grown from lysis-centrifugation fungal isolator blood cultures, which must be specially requested from the laboratory.

Sporotrichosis

Sporotrichosis, caused by the dimorphic fungus *Sporothrix schenckii*, usually arises after soil, moss, or other material that contains the fungus is inoculated into the skin or subcutaneous tissue. Occupations and activities associated with sporotrichosis therefore include gardening, landscaping, farming, and carpentry.

The most common presentation is nodular lymphangitis of one of the extremities. Pulmonary infection develops after inhalation of conidia (asexual fungal spores), usually in a patient with a history of smoking, alcoholism, diabetes, or acquired immunodeficiency syndrome. The chest radiograph typically shows unilateral or bilateral upper-lobe cavities with fibrosis.

At the site of cutaneous inoculation of the fungus a papule develops, which later ulcerates or remains nodular. Chronic fixed cutaneous lesions are commonly found on the face and trunk and tend to be plaques. In rare cases, lesions can involve other areas such as the eye, pericardium, bone, spleen, liver, or meninges. If the classic lymphocutaneous features are absent, the diagnosis is often delayed.

Blastomycosis

Blastomycosis is caused by *Blastomyces dermatitidis*, another dimorphic fungus, which exists in nature in a mycelial phase and converts to a yeast phase at body temperature. Two serotypes of *B dermatitidis* have been identified, depending on the presence or absence of the A antigen.

Blastomycosis is endemic in North America in the Mississippi and Ohio river basins, the Great Lakes region, and a small area in New York and Canada along the St. Lawrence River. Within these areas, blastomycosis has occurred sporadically or in outbreaks. Outbreaks have been associated with occupational and recreational activities, frequently along streams or rivers, which result in exposure to moist soil enriched with decaying vegetation.

Blastomycosis is much less common than histoplasmosis in the United States, and accurate information about its incidence and prevalence is lacking.[2] Cases have also been reported in Africa,[3] India,[4] the Middle East,[5] and South and Central America.[6]

Lymphomatoid granulomatosis

Lymphomatoid granulomatosis, an uncommon disease, is now thought to be a malignant B-cell lymphoma. It usually arises between the ages of 30 and 50 and predominantly affects men. The lung is the organ most often involved, but the skin and central nervous system are also often affected.

Patients commonly present with cough, dyspnea, and skin rash. Skin lesions are raised erythematous rashes, subcutaneous nodules, or ulcers. Neurologic involvement, seen in up to 20% of cases, is manifested by ataxia, cranial nerve abnormalities, and peripheral neuropathy. The diagnosis depends on characteristic histopathologic findings.

Blastomycosis is much less common than histoplasmosis in the United States

Case continued

Although our patient's type of skin lesions, absence of hilar adenopathy, and asymmetrical radiographic presentation argue against histoplasmosis and sarcoidosis, they do not exclude them from consideration.

Our patient does not have any of the common risk factors for pulmonary sporotrichosis except that he is male and his radio-

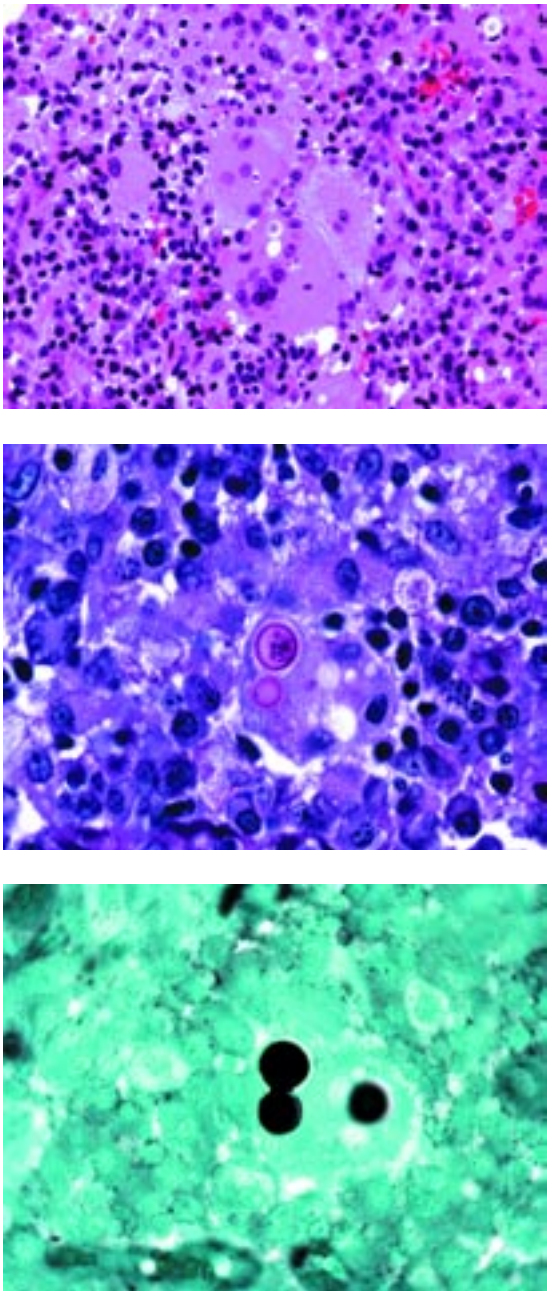

FIGURE 4. Transbronchial lung biopsy specimen showing changes of chronic pneumonia, giant cells, and budding yeast (center of images). Top, hematoxylin-eosin, × 40. Middle, periodic acid-Schiff × 100. Bottom, Gomori methenamine silver × 100.

graphic presentation is also atypical for this disease. Sporotrichosis remains, however, in the differential diagnosis of tuberculosis, fungal infections, and sarcoidosis.[7]

Both blastomycosis and histoplasmosis are endemic in Ohio, but the history did not uncover any the recreational or environmental exposures usually associated with those infections.

A more nodular radiographic appearance of the lung infiltrate would be expected in lymphomatoid granulomatosis, but this disease remains in the differential diagnosis as well.

DIAGNOSTIC TESTS

2 All of the following tests are appropriate except which one?

- ❑ Sputum KOH smear examination
- ❑ Culture of bronchoalveolar lavage and biopsy specimen
- ❑ Serologic tests for fungal organisms
- ❑ Skin biopsy
- ❑ Specific skin testing

All of the above except specific skin testing are appropriate. Reagents for histoplasmin skin testing are no longer available in the United States, and skin-test reactivity is high in endemic areas, thereby limiting its predictive power. No reliable skin test is available for blastomycosis. Skin testing for sarcoidosis (Kveim test) is rarely used because there is no standardized test material approved by the US Food and Drug Administration.

Culture is the gold standard for diagnosing endemic mycoses, but can be slow

Serologic testing

Serologic testing is helpful in diagnosing histoplasmosis, particularly in patients with acute pulmonary symptoms. Complement fixation tests were originally reported to have a sensitivity of 95% in patients with histoplasmosis, although more recent research has reported lower sensitivity of 80% to 90%.[8] Additionally, false-positive tests can be seen in blastomycosis or other fungal infection, or in patients with a persistent antibody response due to a prior *Histoplasma* or other fungal infection.[8,9] An enzyme immunoassay appears to be more sensitive and specific.[10] With any of these serologic tests, a fourfold rise in titer is more diagnostic than a single elevated titer, as titers can persist for years after recovery from infection.

In the case of blastomycosis, available serologic tests of immunodiffusion and complement fixation have poor sensitivity and specificity[11]: a negative test does not rule out

the diagnosis, and a positive titer alone should not be used as the criterion for starting treatment. As with histoplasmosis, a newer enzyme immunoassay appears to be more sensitive and specific for the diagnosis of blastomycosis.[12]

Serologic testing is even less helpful for the diagnosis of sporotrichosis than for other mycoses, except possibly in the analysis of cerebrospinal fluid in patients with chronic meningitis.[13] Newer molecular diagnostic methods, eg, polymerase chain reaction and DNA probes, are likely to be helpful in the future, predominantly because they are more specific.[14,15]

Culture of sputum, tracheal aspirate, bronchoalveolar lavage, tissue biopsy, or bone marrow is the gold standard for establishing the diagnosis of endemic mycoses. However, growth may be delayed for several weeks in the case of histoplasmosis, blastomycosis, or sporotrichosis. Sputum KOH and cytologic examination can be helpful, with a yield of up to 46% for blastomycosis,[11] but it is rarely positive in histoplasmosis.[16]

Case continued

The patient undergoes both bronchoscopic biopsy with lavage and skin biopsy.

The skin biopsy shows broad-based budding yeast, suggestive of blastomycosis.

A KOH smear examination from the lavage specimen is negative.

A biopsy specimen from the right lower lobe shows chronic granulomatous pneumonia containing numerous yeasts with broad-based budding, also compatible with blastomycosis (**FIGURE 4**).

Culture from the lavage specimen is positive for *B dermatitidis* by DNA gene probe.

On further questioning, the patient reveals that he had worked in his mother's garden spreading fertilizer just before his illness began.

Definitive diagnosis of blastomycosis

The definitive diagnosis of blastomycosis requires culture of the fungus from respiratory secretions, tissue, or other infected biologic materials.

B dermatitidis is not difficult to culture, but the process is time-consuming, taking up to 30 days to culture and identify the organism. Thus, although a positive culture confirms the diagnosis, early diagnosis depends on the smear examination of specimens using appropriate stains; seeing the typical budding yeast forms in pathologic specimens combined with a consistent clinical presentation justifies therapy.

The simplest method for rapid diagnosis is by examination of fresh sputum or bronchial washings digested with 10% KOH under a microscope. The yeast is 8 to 20 µm in size and has a characteristic thick, double, refractile cell wall with multiple nuclei and broad-based budding. Although the diagnostic yield of the KOH smear is low, it can be increased by examining multiple specimens.[11,17,18]

Papanicolaou staining of sputum or bronchoscopy specimens is fast and has a high diagnostic yield (> 90%) provided that more than one specimen is examined per patient, both direct staining and concentration for preparation of cell blocks are performed, and the cytopathologists are experienced in identifying fungal pathogens.[18,19] This high sensitivity has therefore not been uniformly reported by all investigators. Some experts have suggested that Papanicolaou smears be more frequently performed by personnel trained to recognize *B dermatitidis*, as this could potentially reduce the need for invasive procedures in patients with suspected pulmonary blastomycosis.[11,20] The organism appears refractile and stains pale blue-green with Papanicolaou stain.

B dermatitidis is often difficult to identify in hematoxylin-eosin-stained histopathologic specimens; therefore, special stains such as Gomori methenamine silver or periodic acid-Schiff are often required.

A study from the Mayo Clinic showed that the diagnostic yield of noninvasive respiratory specimens (86%) was comparable to that of bronchoscopic specimens (92%).[11]

Blastomycosis is a great masquerader

CLINICAL SYNDROMES OF BLASTOMYCOSIS

3 What is the most common clinical manifestation of blastomycosis?

- ❑ Asymptomatic infection
- ❑ Acute or chronic pneumonia
- ❑ Skin lesions
- ❑ Meningitis

At least 50% of cases of blastomycosis are asymptomatic.

Although the clinical presentation of blastomycosis is highly variable, pulmonary manifestations are the most common presenting features. Isolated lung involvement is seen in 70% to 75% of cases, whereas disseminated disease is seen in 25% to 30%.

Pulmonary blastomycosis can be asymptomatic or can present as acute or chronic pneumonia. Pulmonary infection results from inhaling conidia from soil. Conidia that escape the natural defense of neutrophils, monocytes, and alveolar macrophages in the lungs are then converted to the yeast form, which are more resistant to phagocytosis and killing.[21] The tissue response in the lung is described as pyogranulomatous. Once infection is established in the lungs, the hilar lymph nodes may become involved and provide a route for lymphohematogenous dissemination.

The major acquired defense against *B dermatitidis* is cellular immunity, and if the patient's cellular immunity is defective, the organism can spread within the lungs and other sites.

Azoles should never be used in pregnant patients

In acute blastomycosis, radiographs usually reveal lobar or segmental disease; pleural effusion and hilar adenopathy are uncommon. In chronic disease, alveolar or mass-like infiltrates followed by a miliary or reticulonodular pattern are commonly seen. Cavitary disease is not as common as in tuberculosis or chronic cavitary histoplasmosis.[22] In one series of 46 patients with blastomycosis, 32% had a mass and 48% had an alveolar infiltrate on chest radiography.[23] Postinfectious calcifications of lymph nodes or lung parenchyma are rare.

Hematogenous dissemination is common, often to the skin, bones, and genitourinary system.[24] Cutaneous lesions are therefore the next most common manifestations and can be verrucous or ulcerative.[24] These lesions may present with or without concomitant pulmonary lesions. The verrucous form has a raised, irregular border, often with crusting and some drainage, while the ulcerative lesions have a sharp and heaped-up border with a base commonly containing exudate. In disseminated disease, any organ can be involved.

Of importance: blastomycosis is a great masquerader.[20] For instance, pulmonary blastomycosis can present as an acute or chronic disease and can mimic pyogenic bacterial pneumonia, other fungal infections, tuberculosis, or bronchogenic carcinoma. Similarly, the skin lesions can be mistaken for skin cancer.

Acute disease often presents as an influenza-like illness characterized by fever, arthralgia, myalgia, and cough that may be associated with mucopurulent sputum.[25] Other patients with acute presentations may experience an abrupt onset of pleuritic chest pain lasting about 48 hours, unaccompanied by fever or other constitutional symptoms. Severe illness characterized by diffuse pulmonary infiltrates and severe hypoxemia has been reported.[26]

Chronic pulmonary infection typically presents with a 2-month to 6-month history of fever, night sweats, productive cough, and chest pain.

TREATMENT OF BLASTOMYCOSIS

4 What is the appropriate initial course of action for this patient?

- ❑ Outpatient observation for possible spontaneous resolution
- ❑ Outpatient treatment with itraconazole 200–400 mg/day
- ❑ Outpatient treatment with ketoconazole 400–800 mg/day
- ❑ Outpatient treatment with fluconazole 400–600 mg/day
- ❑ Admission for intravenous amphotericin 1.5–2.5 g total dose

The patient is admitted for initial treatment with amphotericin because of clinical and pathologic evidence of dissemination with extrapulmonary skin involvement and progression of the pulmonary disease over 1 month.

However, in current clinical practice, many patients with this kind of pulmonary and skin presentation and without evidence of dissemination to other organs would be treated with itraconazole. Amphotericin B, the drug of choice before the azoles became available, is increasingly reserved for severely ill or immunocompromised patients or for suspected central nervous system involvement.

TABLE 1

Not available for online publication.
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Although blastomycosis can spontaneously resolve within 4 weeks or so in an immunocompetent host, most cases require therapy. It is very important to make sure there is no extrapulmonary involvement before choosing a watch-and-wait approach. Indications for treatment include an immunocompromise, extrapulmonary disease, and progressive or life-threatening infection; some experts also believe that treatment should be started whenever the diagnosis is suspected, because some patients with apparent spontaneous resolution may present with progressive disease at a later time.[27] Disseminated infection should prompt an immunologic evaluation, including testing for human immunodeficiency virus.

Treatment options include amphotericin B, ketoconazole, itraconazole, and fluconazole (**TABLE 1**). No randomized blinded studies have compared these agents for the treatment of blastomycosis.

Amphotericin B is the treatment of choice for patients who are immunocompromised, have life-threatening or central nervous system disease, or for whom azole therapy has failed. It is the only drug approved for blastomycosis in pregnant women, whereas the azoles should never be used in pregnant patients because of their embryotoxic and teratogenic potential.

After the disease is stabilized with amphotericin B, therapy can be switched to oral itraconazole. Although there are no comparative trials, itraconazole appears to be more effective than either ketoconazole or fluconazole. In a prospective trial, 95% of patients receiving itraconazole at 200 to 400 mg per day for at least 2 months were cured.[28] Patients with mild to moderate disease that does not involve the central nervous system should be treated with itraconazole for a minimum of 6 months; bone disease may require longer therapy.[29]

Alternatives to itraconazole include 6 months of either ketoconazole or fluconazole, although the doses of fluconazole must be higher than the usual dose, and ketoconazole may be less well tolerated than itraconazole.[27]

The newest azole, voriconazole, appears to be effective and may also be a treatment for central nervous system disease in the future.

CASE RESOLUTION

After receiving two doses of intravenous amphotericin, the patient develops mild renal insufficiency. He is then started on itraconazole 200 mg by mouth twice a day with a plan to continue this regimen for 6 months. His cough clears and his skin lesions regress. A follow-up chest radiograph 2 weeks after discharge shows persistent but improved infiltrates in the right lower lobe. On his last follow-up visit 5 months after the initial presentation, his radiographic and skin lesions have completely resolved.

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