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**Cervicofacial actinomycosis: a long forgotten infectious complication of
immunosuppression - report of a case and review of the literature**

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Actinomycosis is a rare chronic granulomatous infection caused by Gram-positive, non-acid-fast, anaerobic to microaerophilic bacteria. We report a case of cervicofacial actinomycosis in an 86-year-old woman undergoing immunosuppressive therapy with azathioprine and prednisone for rheumatoid arthritis. She underwent a dental treatment several months earlier. The diagnosis of culture-negative actinomycosis was based on histopathology findings and the isolation of companion bacteria. The patient was treated with amoxicillin-clavulanic acid for 3 months, which produced complete clearance of her cervicofacial actinomycosis. Our case points out the pitfalls of diagnostic procedures in actinomycosis and the ability of this rare disease to mimic other medical conditions.



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Photo Vignette

Cervicofacial actinomycosis: a long forgotten infectious complication of immunosuppression - report of a case and review of the literature

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Abstract

Actinomycosis is a rare chronic granulomatous infection caused by Gram-positive, non-acid-fast, anaerobic to microaerophilic bacteria.

We report a case of cervicofacial actinomycosis in an 86-year-old woman undergoing immunosuppressive therapy with azathioprine and prednisone for rheumatoid arthritis. She underwent a dental treatment several months earlier. The diagnosis of culture-negative actinomycosis was based on histopathology findings and the isolation of companion bacteria. The patient was treated with amoxicillin-clavulanic acid for 3 months, which produced complete clearance of her cervicofacial actinomycosis.

Our case points out the pitfalls of diagnostic procedures in actinomycosis and the ability of this rare disease to mimic other medical conditions.

Key words: actinomycosis, *Actinomyces* spp, cervicofacial actinomycosis, bacterial infection

Case synopsis

An 86-year-old woman presented at our outpatient clinic with a one-month history of a progressive, painful swelling on the left cheek. She received oral amoxicillin-clavulanic acid 1g twice daily over 10 days, with little effect. The patient was in good health and constitutional symptoms were denied. Her medical history included rheumatoid arthritis, which was treated with azathioprine 50mg/day and prednisolone 7.5mg/day. Any trauma to the cheek was denied, but she underwent a dental treatment a few months earlier. Clinically there was an indurated plaque, 5cm in diameter, with three red bluish nodules on the left cheek, some of which were ulcerated (Figure 1A). Cervical lymphadenopathy was not palpable.

A skin biopsy was performed showing a deep inflammatory infiltrate and epithelial lamellas, which suggested the diagnosis of a ruptured epidermoid cyst. There was no evidence of a malignant process. Histological stains for pathogens (PAS, Ziehl-Neelsen) were negative; Brenn-Brown stain revealed bacteria-like structures. Both broad spectrum bacterial PCR from the skin biopsy and aerobic and anaerobic tissue cultures were all negative. A cellular test for tuberculosis (QuantiFERON gold) was also negative. An MRI of the head suggested an inflammatory process of the soft tissue deriving from a maxillary sinus.

Owing to growth of the skin lesion over the next four months the patient was referred for further investigations to our inpatient clinic. Physical examination of the left cheek showed multiple, red-bluish, partially ulcerated nodules, which on pressure discharged purulent material. In addition, an indurated, firm plaque measuring approximately 7cm in diameter was palpable (Figure 1B). The clinical differential diagnosis included a malignant process, an odontogenic fistula, a disrupted epidermal cyst, cutaneous sarcoidosis, cutaneous tuberculosis with fistulae (scrofuloderma), or other deep infections. A deep skin biopsy was performed, which showed a massive dermal, predominantly neutrophilic infiltrate forming abscesses (Figure 1D). Sulfur granules appeared among the infiltrate (Figure 1d,e,f). Brown-Brenn staining revealed Gram-positive and PAS-positive filamentous, radially oriented structures at the periphery of these granules (Figure E,F). Bacterial cultures remained negative. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* were detected by 16S rDNA-broad spectrum PCR. Both bacteria are commonly found as bystander organisms in cervicofacial actinomycosis and finally enabled us to establish the diagnosis.

The patient was started on intravenous amoxicillin-clavulanic acid (2,2g TID) for 2 weeks. After a significant clinical regression of the lesions, the therapy was changed to oral amoxicillin-clavulanic acid (625mg bid) for 10 weeks. Under this treatment all nodules and the firm subcutaneous plaque fully resolved, leaving only focal hyperpigmentation and discrete scars (Figure 1C).

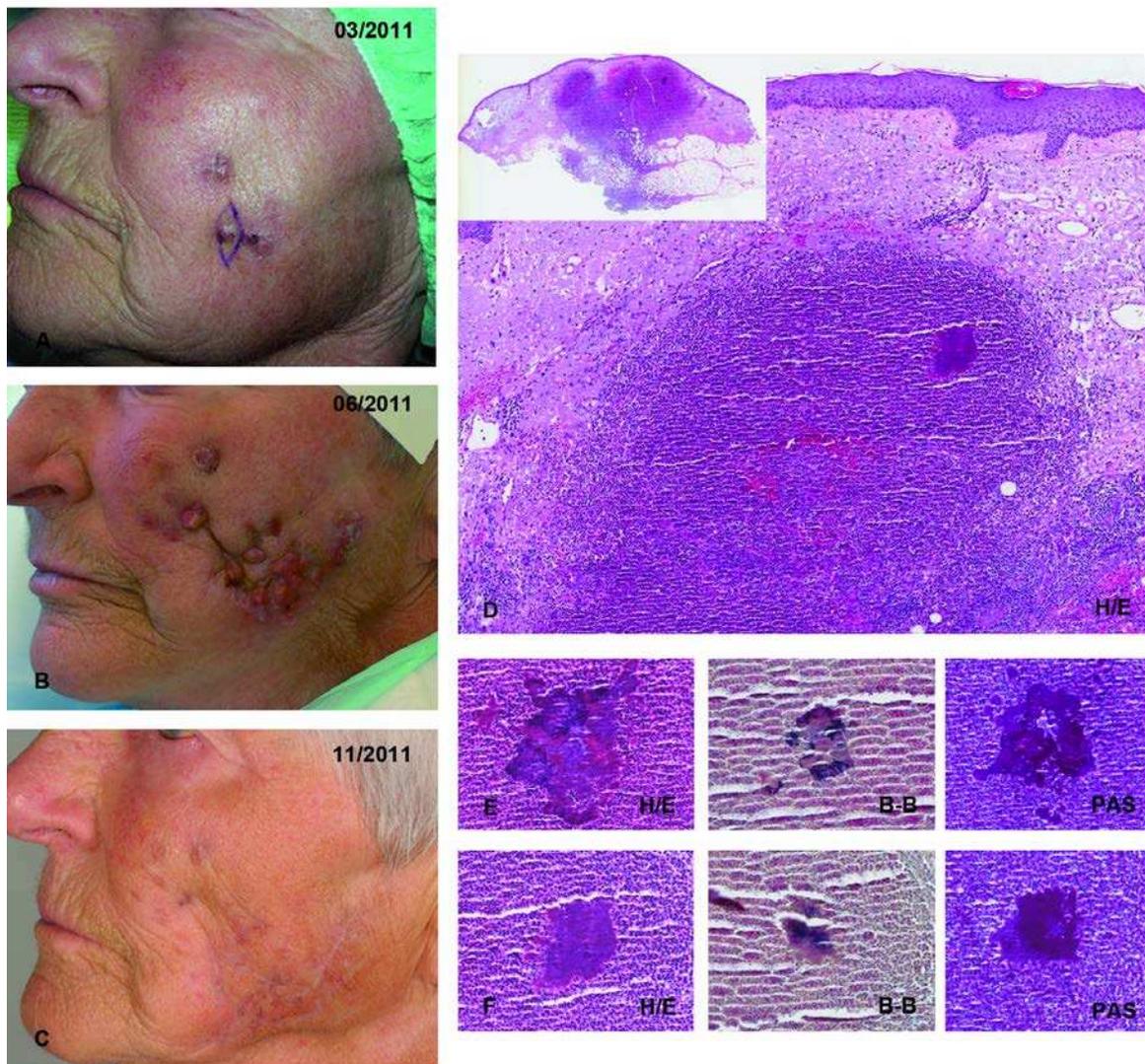


Figure 1

Figure 1. Clinical and histological presentation of cervicofacial actinomycosis: Panels A, B, C show the evolution of skin lesions over nine months (time points are marked). Panel D shows overview histology (upper left panel, hematoxylin and eosin staining, original magnification x0.6) and massive dermal inflammatory infiltrate consisting predominantly of neutrophils and round homogenous eosinophilic structures, known as sulfur bodies (hematoxylin and eosin staining, original magnification x4). Panels E and F reveal characteristic of sulfur bodies using

Comment

Actinomycosis is a rare, chronic and slowly progressive infection caused by Gram-positive, non-acid-fast, anaerobic to microaerophilic bacteria. Owing to their filamentous structure Actinomyces were originally considered fungi. Actinomyces are commensals of the human oropharyngeal, respiratory, gastrointestinal, and urogenital tracts. Cervicofacial actinomycosis, also called “lumpy jaw syndrome,” is the most common form caused by *Actinomyces israelii* and comprises about 50% of all reported cases [1,2] It usually follows dental treatments, although it can arise spontaneously in patients with poor dental hygiene. Actinomycosis is clinically often misdiagnosed because it can mimic numerous infectious and non-infectious diseases, including malignant tumors. The typical presentation of cervicofacial actinomycosis is a painless or painful soft tissue swelling. Direct spread into the adjacent tissue can develop over time, along with development of fistulas that discharge purulent material containing typical yellow sulfur granules. Other variants of actinomycosis include thoracic, abdominopelvic, central nervous system, musculoskeletal, and disseminated infection. Even though actinomycosis is not considered an opportunistic infection, it has been described in individuals with impaired immune systems, as in HIV disease or leukemia [3, 4]. There is no predilection for age, race, season or occupation.

Diagnosis of actinomycosis requires correlation of histopathological and microbiologic findings. The cornerstone of the histological diagnosis of actinomycosis is the presence of the so-called “sulfur granules” or Splendore-Hoeppli phenomenon (Figure histology) in crumbly, pus-resembling secretions [5]. Sulfur granules are bacterial colonies that appear as round or oval eosinophilic masses with basophilic terminal “clubs” on hematoxylin-eosin stained sections. However, sulfur granules are not specific for actinomycosis because they represent a localized immunologic response to an antigen-antibody precipitation occurring in infectious (e.g. fungi, parasites and bacteria) or other non-infectious processes (e.g. around inert material, in hypereosinophilic syndrome and allergic conjunctival granuloma) [6]. Direct isolation of actinomyces from a clinical specimen or from sulfur granules is necessary for a definitive diagnosis. However, the failure rate for isolation via anaerobic culture is high owing to previous antibiotic treatment, inadequate methodology, or overgrowth of the slow growing actinomyces by bystander organisms like *Bacteroides*, *Fusobacterium*, or *Aggregatibacter* [2]. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* are oral bacteria indigenous to the human oral cavity, which are common bystander bacteria of cervicofacial actinomycosis. Because sequencing of the 16S rDNA gene has become a reference method for bacterial identification [7], it also became possible to identify such bystander bacteria that are difficult to cultivate. In our patient, the results of 16S rDNA gene amplification and sequencing were negative for *Actinomyces* spp., but *Fusobacterium nucleatum* and *Porphyromonas gingivalis* could be sequenced. This constellation of findings supported the diagnosis of actinomycosis, without direct detection of actinomyces.

Actinomyces spp. are sensitive to penicillin and this antibiotic represents the first line treatment [1, 2]. Penicillin G is the drug of choice for treating actinomycosis and development of resistance during prolonged therapy is rare. The combination of penicillin and a beta-lactamase inhibitor offers the advantage of treating the beta-lactamase producing bystander organisms as well. The antibiotic regimen should initially be administered intravenously until clinical improvement is demonstrated, followed by oral administration over 2–12 months. The patients’ response to therapy indicates the duration of treatment. Surgery is only necessary in cases with formation of necrotic tissue, soft tissue abscesses requiring drainage, or excessive scar and fistula formation. The prognosis for treated cervicofacial actinomycosis is excellent [3].

In conclusion, we report a case of actinomycosis in which the diagnosis was established by combining histopathology findings and the isolation of companion bacteria, without direct isolation of *Actinomyces* spp. Our case points out the pitfalls of the diagnosis of actinomycosis. Physicians should be aware of the many faces of actinomycosis and the difficulty of detecting *Actinomyces* in clinical samples.

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