Clinical Actinomycosis: Misdiagnosis of Cranial Bone Tumor – A Case Report

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ABSTRACT

Background: Actinomycosis is a rare infection, frequently misdiagnosed as a neoplasia. This chronic and granulomatous disease is caused by Actinomyces israelii species. Cervicofacial actinomycosis occurs in 60% of cases and the diagnosis is commonly made by histopathology study.

Case Description: We report a case of fronto-orbital osteomyelitis initially misdiagnosed as a cranial bone meningioma, but later proved to be a case of actinomycosis. ⁹⁹m⁹⁹m Technetium (⁹⁹m⁹⁹m Tc) three-phase bone single-photon emission computed tomography/computed tomography (SPECT/CT) and ⁹⁹m⁹⁹m Tc-ubiquicidin (UBI) 29-41 bone SPECT/CT scans were performed to corroborate the control of the infection.

Conclusion: Craniofacial actinomycosis is the most common presentation of actinomycosis. However, it continues to be a rare and difficult disease to diagnose and is often confused with a neoplastic process. The ⁹⁹m⁹⁹m Tc-UBI 29-41 bone SPECT/CT scan could be an auxiliary noninvasive diagnostic alternative and a follow-up method for these patients.

Keywords: Actinomyces, Craniofacial, Osteomyelitis

INTRODUCTION

Actinomycosis is a rare invasive bacterial disease that causes a chronic, suppurative, granulomatous infection. Actinomyces israelii are Gram-positive, anaerobic, filamentous bacilli that have low pathogenicity and normally colonize the mouth and gastrointestinal tract.[10] This disease can affect multiple anatomical sites, being the cervicofacial presentation (60%) the most frequent[17,22,25] followed by the thoracic pulmonary (30%) and abdominopelvic (20%). Central nervous system (CNS) involvement is less common.[10,11,20] This disease can mimic neoplastic processes, tuberculosis, nocardiosis,[12,29] and even fibrous dysplasia.[11] In consequence, the diagnosis of actinomycosis is challenging and the disease is frequently overlooked.

Given that actinomycosis is a purulent bacterial infection, radiotracers which detect bacteria colonization have diagnosis potential. Recent reports have showed that ⁹⁹m⁹⁹m technetium-ubiquicidin...
(99mTc-UBI) 29-41 bone single-photon emission computed tomography/computed tomography (SPECT/CT) scan can be a useful diagnostic study for pyogenic vertebral osteomyelitis. This radiotracer can differentiate inflammatory from infectious processes.

The diagnosis of actinomycosis is made by a positive culture or the visualization of necrosis with sulfur granules and Gram-positive filamentous bacteria in the histopathology study. Therapy consists in high doses of penicillin's G or amoxicillin for long periods of time (6–12 months).

CASE DESCRIPTION

A 57-year-old woman from Torreon Coahuila was referred in November 2015 for sudden increase in volume of the right fronto-orbital region. The patient reported a contusion in the right frontal region 1 month before and was underwent treatment with metronidazole but not improvement was observed [Figure 1a-c].

Relevant antecedents included cardiothoracic surgery at 4 years old to treat an unspecified cyanotic heart condition and in 1992 plastic surgery established the diagnosis of "craniofacial dysostosis" and a fronto-orbital advancement, including osteotomies and bone cranial remodeling with methyl methacrylate.

In January 2016, a magnetic resonance imaging study reported heterogeneous enhancement mass in the bilateral fronto-orbital region [Figure 2a-c] Pre-surgical MRI and [Figure 2d-f] post-surgical CT scan, control 6 months after surgery, causing significant craniofacial deformation a malignant neoplastic process was suspected. Bone meningioma (an atypical location) [Table 1], bone metastasis, and monostotic fibrous neoplasm were considered into the differential diagnoses. During screening for a primary tumor, a thoracic abdominal CT scan was performed. In May 2016, a highly vascularized hyperostotic lesion was partially resected. This procedure was aborted as consequence of an important intraoperative hemorrhage. Pathology reported fibroconnective tissue with hemorrhage, fibrin, and unspecified polymorphonuclear inflammatory infiltrate. As the craniofacial bone deformity worsened with bilateral ocular extension, a second partial resection was performed in September 2016. Histopathological findings included a multifocal foreign body-type granulomatous lesion and granulation tissue [Figure 3].

The culture was reported negative, but tissue staining with hematoxylin and eosin revealed bacilli compatible with A. israelii was isolated in the tumor tissue by histopathological study by staining for hematoxylin and eosin [Figure 3]. Amoxicillin-clavulanic acid 3 times a day was initially indicated and followed by intramuscular benzathine penicillin's every 2 weeks for 6 months. At the end of the treatment, infectious remission had been achieved. In 2017, the supraorbital methyl methacrylate bar was surgically removed [Figure 4a and b]. No recurrence of the deformity was identified in the follow-up visits. In February 2020, 99mTc three-phase bone SPECT/CT scan and 99mTc-UBI 29-41 bone SPECT/CT scan was performed, and a negative infection result was reported [Figure 4c and d].

DISCUSSION

Cervicofacial or craniofacial Actinomyces is the most common presentation of actinomycosis, accounting for 60% of cases [Tables 1 and 2]. Brain abscesses are the rarest and most serious presentation of the infection by A. israelii. Bonnefond et al.[4] reported a series of 28 patients with A. israelii, including five cases with orocervicofacial presentation (17%) and one patient with intracranial involvement. In 92% of cases, the diagnosis was not suspected at admission. This infection frequently misdiagnosed with neoplastic processes, such as meningioma, granulomas, and osteomyelitis secondary to tuberculosis or nocardiosis. In the present case, we did not consider actinomycosis in the initial differential diagnosis. However, it is important to suspect this entity in cases with recurrent craniofacial deformations and a history.

Figure 1: (a) Presurgical images, significant bilateral fronto-orbital defect, predominantly right side. (b and c) control 3 years after surgery, significant remission of bone deformity.
of dental extractions with alveolar abscesses,[16,26] otological surgeries, and reconstructive surgeries with prosthetics as methyl methacrylate.

A positive uptake with $^{18}$F-fluorodeoxyglucose positron emission tomography/CT,[14] technetium-99m-methoxyisobutylisonitrile and Thalio-201[15] has been reported in cases of actinomycosis infection with a previous misdiagnosis of neoplastic disease. However, UBI 29-41 is an antimicrobial peptide with greater effectiveness against

Figure 2: (a-c) (Upper quadrants) Presurgical gadolinium-enhanced T1-weighted magnetic resonance imaging showing heterogeneous enhancement mass in the bilateral fronto-orbital region predominantly on the right side, we can see a hypodensity in relation to methyl methacrylate. (d-f) (Lower quadrants) Computed tomography scan control 6 months after the medical treatment with resolution of the deformity.

Figure 3: Hematoxylin and eosin staining. Basophilic structure, granular, and peripheral-pseudopalisading, hemorrhagic background, and peripheral lymphocytic and polymorphonuclear infiltrate.

Figure 4: (a and b) 3D computed tomography (CT) scan showing silicone implants in the chin and zygomatic bone, a supraorbital methyl methacrylate bar and plates in the bilateral parietal region (upper quadrants). (c and d) (Lower quadrants): $^{99m}$technetium-Ubiquicidin (29–41)/three-phase bone single-photon emission computed tomography/CT scan control 3 years after the last surgical intervention showing diffuse uptake of the radiotracer, suggestive of an inflammatory process, an active infectious process is ruled out.
Table 1: Published cases of craniofacial *Actinomyces* with misdiagnosis of meningioma.

| Reference | Year | Sex, Age | Localization of Meningioma | Risk factors | Onset of symptoms | Clinical findings | Diagnosis of actinomycosis | Surgery | Medical treatment | Recovery |
|-----------|------|----------|-----------------------------|--------------|-------------------|------------------|------------------------|---------|------------------|---------|
| Khosla[12] | 1984 | 71, M    | Parasagittal (right frontal) | NE           | 5 years           | Forgetfulness     | Histology              | Bifrontal craniotomy | Crystalline penicillin's and erythromycin for 3 months | Remission |
| Chopra[3]  | 1995 | 65, M    | Right occipital extending to the tentorium. | TBI, retroauricular injury | 30 years | Headache, Vertigo, unsteady gait, nystagmus, papilledema | Histology | Craniotomy and partial resection | Chloramphenicol 500 mg/day + Ceftriaxone 1 g IM for 6–12 months | Not specified |
| Deora[8]   | 2018 | 47, F    | Meningioma en plaque in maxilla, temporal base, sphenoid, and zygoma | NE           | 1 year            | Restriction of mouth opening and right NC III palsy. | Histology | Surgical decompression | Antitubercular therapy | No recovery. Dead |
| Kobayashi[13] | 2020 | 67, F    | Left superior orbital | COPD         | 1 year            | Recurrent swelling and erythema around in the left eye, Orbital mass | Histology, PCR | Anterior orbitotomy with excision biopsy of the mass + debridement of left orbital roof | TMP/SMX for 12 days + Ceftriaxone for 2 weeks | Remission |

TBI: Trauma brain injury, COPD: Chronic obstructive pulmonary disease, TMP/SMX: Trimethoprim/sulfamethoxazole.
| Reference | Year | Age | Sex | Location of infection | Risk factors | Diagnosis | Medical treatment | Surgical procedures | Neutrophil imaging studies | Spect/CT scan | Clinical findings | Recovery |
|-----------|------|-----|-----|-----------------------|--------------|-----------|------------------|-------------------|-----------------------|--------------|-----------------|---------|
| Bolano et al. [10] | 1993 | M | 57 | Temporal lobe | Arterial occlusion | Bone osteomyelitis | Gram stain, culture, PCR | Biopsy | CT scan | Could not be determined | Asymptomatic | Remission, no recurrence |
| Yoneda et al. [11] | 1999 | M | 28 | Paranasal sinus | Chronic sinusitis | Paranasal sinusitis | Culture, CT scan | Biopsy | CT scan and MRI | No | No | Recovery |
| Solarz et al. [12] | 2000 | M | 60 | Neck | Hypothyroidism | Thyroiditis | Culture, CT scan | Biopsy | CT scan | No | No | Asymptomatic |
| Chatterjee et al. [13] | 2001 | M | 56 | Temporal lobe | Malignant hypertension | Brain abscess | Culture, CT scan | Biopsy | CT scan | No | No | Remission, no recurrence |
| Hwang et al. [14] | 2002 | M | 55 | Temporal lobe | Congenital heart disease | Temporal lobe abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |
| Nomura et al. [15] | 2003 | M | 72 | Parotid gland | Diabetes mellitus | Parotid abscess | Culture, CT scan | Biopsy | CT scan | No | No | Remission, no recurrence |
| Apil et al. [16] | 2004 | M | 65 | Temporal lobe | Epilepsy | Temporal lobe abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |
| Pant et al. [17] | 2005 | M | 45 | Mandible | History of trauma | Mandible abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |
| Saras et al. [18] | 2006 | M | 50 | Temporal lobe | Prior surgery | Temporal lobe abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |
| Chaterjee et al. [19] | 2007 | M | 60 | Temporal lobe | Prior surgery | Temporal lobe abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |
| Ohkawara et al. [20] | 2008 | M | 30 | Temporal lobe | History of trauma | Temporal lobe abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |
| Hwang et al. [21] | 2009 | M | 65 | Temporal lobe | Prior surgery | Temporal lobe abscess | Culture, CT scan | Biopsy | CT scan | MRI, USG, CT scan | No | No | Remission, no recurrence |

**NE:** Not specified, Cefx: Cefuroxime, Ceft: Ceftriaxone, Met: Metronidazole, Clind: Clindamycin, FNAB: Fine-needle aspiration biopsy, Amox: Amoxicillin, Ampi/Sul: Ampicillin/Sulbactam, Teico: Teicoplanin, Levo: Levofloxacin, Moxi: Moxifloxacin, Cefp: Cefepime, PIV: Intravenous penicillin's, PO: Oral penicillin's, Chlo: Chloramphenicol, Est: Streptomycin, SPECT/CT scan: 3-phase bone SPECT/CT scan, PneumoEnc: Pneumoencephalogram, AngCarot: Carotid angiogram, HIC: Immunohistochemistry, TMP: Temporomandibular joint disorders, PET: Positron emission tomography, FDG: Fluorodeoxyglucose, Cervical lymph node and upper parotid lymph node biopsies.
bacterial diseases.[23] $^{99m}$Tc-UBI 29-41 bone SPECT/CT scan is an useful radiotracer in the diagnosis of pyogenic vertebral osteomyelitis[9,15,9,15] with a high sensitivity and specificity (96.3% and 94.1%, respectively).[7] Diagnostic accuracy for osteomyelitis is 100% in studies with $^{99m}$Tc-UBI 29-41 bone SPECT/CT scan versus 90% reported in $^{99m}$Tc three-phase bone SPECT/CT scan.[23] We performed $^{99m}$Tc three-phase bone SPECT/CT and $^{99m}$Tc-UBI 29-41 bone SPECT/CT scans as part of the follow-up protocol in this patient, to screen for signs of active infection. Nevertheless, no reports have been found in literature about the use of radiopharmaceuticals in cranial osteomyelitis diagnosis. However, we consider that they could be a promising auxiliary diagnostic and follow-up method in patients with confirmed craniofacial actinomycosis although more studies are required.

A positive actinomycosis culture occurs in 50% of cases. Therefore, diagnosis is generally made by histology.[24] Bonnefond et al.[4] reported a series with 50% of cultures positive for A. israelii. In contrast, only 42% of histopathological studies were positive, even though 71% of the patients underwent a biopsy. However, most of the cases had an abdominopelvic presentation (9/28) and only five patients had a craniofacial disease. A positive culture in cases with craniofacial or CNS presentation was uncommon[5,21,23] and the diagnosis was made by histopathology sand immunohistochemistry[10] or PCR[16] for A. israelii.

Patients with actinomycosis require high doses of penicillin's G or amoxicillin for long periods of time (6–12 months), but the duration of antimicrobial therapy could be reduced to 3 months in patients with total surgical resection.[24] In Bonnefond et al.[4] study, a treatment with amoxicillin for approximately 120 days (range 60–180) was indicated. Metronidazole has not demonstrated effectiveness in craniofacial A. israelii[24] and therefore should not be used. In the case here presented, penicillin's treatment of 100–200 mg/kg per doses was maintained for 6 months. This patient progression was controlled and resolution was achieved only after targeted antibiotic treatment was established.

CONCLUSION

- Craniofacial actinomycosis is the most common presentation of actinomycosis. However, it continues to be a rare and difficult disease to diagnose and is often confused with a neoplastic process.
- Resective surgery still plays an important role for diagnosis, while chronic treatment with high-dose penicillin's remains the therapeutic pillar to control the disease and prevent recurrence.
- Histology is the cornerstone diagnostic study in patients with craniofacial presentation.
- $^{99m}$Tc-UBI 29-41 bone SPECT/CT scan is a noninvasive study that identifies bacterial infection and could be play an auxiliary role in the diagnosis and follow-up of these patients.

Acknowledgments

None.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: De la Cerda Vargas MF, Rangel JA, Mata EM, Ramírez-Cárdenas A, Sandoval-Bonilla BA. 99m Tc-UBI 29-41 bone SPECT/CT scan in craniofacial actinomycosis: Misdiagnosis of cranial bone tumor – A case report. Surg Neurol Int 2020;11:442.