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Case Report

^{99m}Tc-UBI 29-41 bone SPECT/CT scan in craniofacial *Actinomyces israelii*: 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. ^{99m}Technetium (^{99m}Tc) three-phase bone single-photon emission computed tomography/computed tomography (SPECT/CT) and ^{99m}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 ^{99m}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.[4] 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,[22,25] 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 ^{99m}technetium-ubiquicidin

(^{99m}Tc-UBI) 29-41 bone single-photon emission computed tomography/computed tomography (SPECT/CT) scan can be a useful diagnostic study for pyogenic vertebral osteomyelitis.[9,15] This radiotracer can differentiate inflammatory from infectious processes.[7]

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.[24] Therapy consists in high doses of penicillin's G or amoxicillin for long periods of time (6–12 months).[24]

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, ^{99m}Tc three-phase bone SPECT/CT scan and ^{99m}Tc-UBI 29-41 bone SPECT/CT scan was performed, and a negative infection result was reported [Figure 4c and d].

DISCUSSION

Cervicofacial[5,19,21,26] or craniofacial[1,16,18,23] *Actinomyces* is the most common presentation of actinomycosis, accounting for 60% of cases [Tables 1 and 2].[17,22,25] Brain abscesses are the rarest and most serious presentation of the infection by *A. israelii*.[3,10,11] 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,[6,8,12,13] granulomas, and osteomyelitis secondary to tuberculosis or nocardiosis.[22,25] 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.

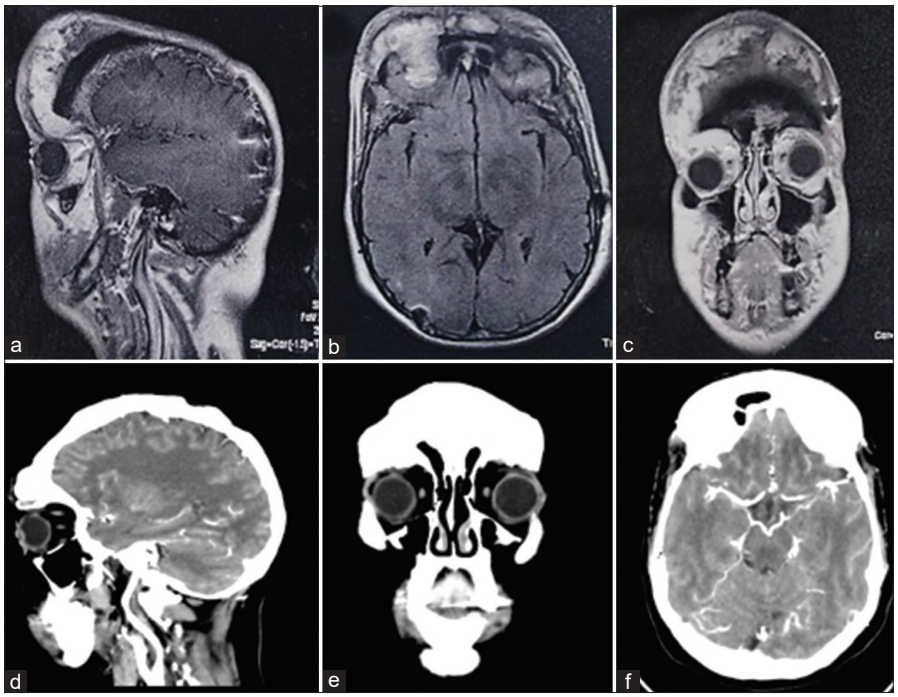

Figure 2: (a-c) (Upper quadrants) Presurgical gadolinium-enhanced T1-weighted magnetic resonance imaging showing heterogeneous enhancement mass in the bilateral fronto-orbital region predominantly on the right side, we can see a hypodensity in relation to methyl methacrylate. (d-f) (Lower quadrants)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

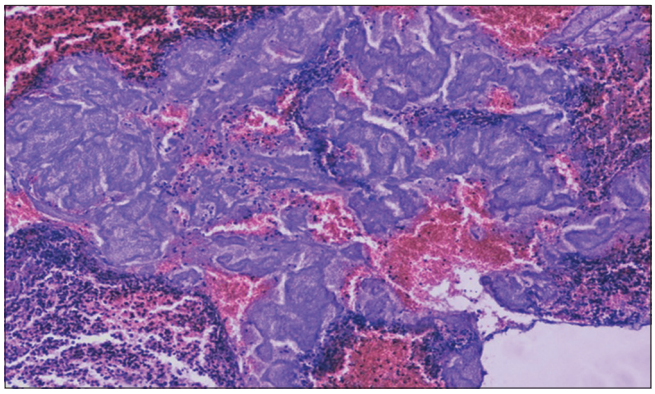

Figure 3: Hematoxylin and eosin staining. Basophilic structure, granular, and peripheral-pseudopalisading, hemorrhagic background, and peripheral lymphocytic and polymorphonuclear infiltrate.

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] tecnetium-99m-methoxyisobutylisonitrile and Thalio-201[2] 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

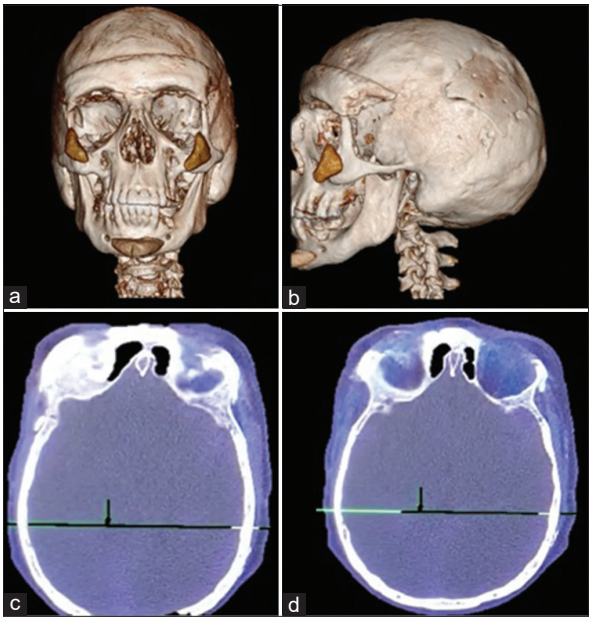

Figure 4: (a and b) 3D computed tomography (CT) scan showing silicone implants in the chin and zygomatic bone, a supraorbital methyl methacrylate bar and plates in the bilateral parietal region (upper quadrants). (c and d) (Lower quadrants): ^{99m}technetium-Ubiquicidin (29–41)/three-phase bone single-photon 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 Confusion Seizures Headache Nausea Hemiparesis Papilledema	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 Oral amoxicillin for 6 months	Remission

TBI: Trauma brain injury, COPD: Chronic obstructive pulmonary disease, TMP/SMX: Trimethoprim /sulfamethoxazole.

Table 2: Cases reported with craniofacial and CNS *Actinomyces israelii*.

Reference	Year	SEX, Age	Location of infection	Risk factors	Clinical findings	Neuroimaging studies	SPECT/CT scan	Diagnosis	Surgery	Medical treatment	Recovery
Bolton[5]	1964	17, F	Temporal lobe abscess, middle cranial fossa	NE	Fatigue Anorexia Headache Drowsiness Dental and jaw pain Neck stiffness Facial paralysis Paresis	Rx CT scan EEG PneumoEnc AngCarot	No	Culture	Temporary abscess drainage	Oral Chlo 250 mg every 6 h Oral Tet 200 mg every 4 h PIV 1000 IU IM every 2 h	Recurrence
Yenson[26]	1983	57, M	Facial osteomyelitis	Molar extraction	Eye drainage Eye and face edema.	CT scan	No	Histology	Debriding and drainage surgeries by maxillo and oral	Chlo, Est, and P for long time PIV for 2 weeks, PO for 6 months	Remission
Ajal[1]	1997	10, M	Otomastoid	Tympanic ventilation tube	Otorrhea	CT scan	No	Histology	Resection of a polyp in the ear	PIV for 4 weeks, POV for 3 months	Remission, Asymptomatic
Soto-Hernandez[23]	1999	28, F	Cranial (parietal) + epidural abscess	NE	Fever Headache Threw up Convulsions Papilledema Meningeal signs	CT scan and MRI	No	Culture	Parietal craniotomy + epidural abscess drainage	Ceft and Met IV Oral Clind 600 mg for 6 months	Remission, Asymptomatic
Pant[19]	2008	40, M	Facial	NE	Facial edema	MRI	No	Histology	FNAB, Deforming scar reconstruction	PO 250 mg for 12 weeks	Remission
Nomur[16]	2011	44, M	Skull base and craniocervical junction	Tooth extraction and Alveolar abscess	Diplopia Fever Cervical edema	CT scan and MRI, FDG-PET	No.	Histology PCR	Cervical lymph node and clivus biopsy *	PIV 18 million for 6 weeks PO for 6 months	Remission, No neurological deficit
Shah[21]	2013	45, M	Cervicofacial	NE	Facial edema suppuration Dental pain trismus	OP	No	Culture, Histology	Debridement +Extraction of third molars.	PIV G 1 million IU for 4 weeks Amox/Ac for 3 months	Remission
Chatterjee[5]	2015	13, M	Cérvicofacial	None	Nódulo infra-auricular	OP, RX, USG y CT scan	No	Histology	Biopsy partial resection of the mandible and parotid + mandibular plate	Cefx 500 mg every 12 h Met 200 mg every 8 h	NE Lost follow up
Oukessou[18]	2015	30, M	Temporal bone	Chronic smoker, Pulmonary TB	Otorrhea NC VII paralysis Anacusia	CT scan	No	Histology	Mastoid biopsy. Mastoidectomy	Amox/Ac for 2 weeks Topic Fq for 1 month Oral Amox 4 g/day for 5 months	Recurrence Facial paralysis.
Ham[10]	2011	60, M	Brain abscess	No	Alteration of mental functions Coma	MRI Spectroscopy PET-CT	No	Histology HIC	Biopsy	Ampi/Sul IV	Remission Neurological status did not improve
Hwang[11]**	2018	51, M	Brain abscess temporal lobe and temporal bone, pterygopalatine fossa, skull base and sphenoid wing	Multiple dental procedures. Condylectomy and coronoidectomy for TPM. *Actinomyces* craniofacial (nasopharynx)	Trismus TPM Headache Facial hypoesthesia	CT scan MRI Nasal endoscopy	No	Histology	Endoscopic nasal biopsy + Brain abscess drainage	PIV G 20 Million IU day for 6 weeks Oral amoxi every 8 hours for 6 months Management in relapse Teico 400 mg/day Moxi 400 mg/day Cefp 100 mg every 12 hrs + Levo 500 mg/day for 6 months	Remission

NE: Not specified, Cefx: Cefuroxime, Ceft: Ceftriaxone, Met: Metronidazole, Clind: Clindamycin, FNAB: Fine-needle aspiration biopsy, Amox: Amoxicillin, Amox/Ac: Amoxicillin-clavulanic Acid, Fq: Fluoroquinolone, Sulfa: Sulfadiazine, Tet: Tetracyclines, Ampi/Sul: Ampicillin/Sulbactam, Teico: Teicoplanin, Levo: Levofloxacin, Moxi: Moxifloxacin, Cefp: Cefpodoxime, P: Penicillin's, PIV: Intravenous penicillin's, PO: Oral penicillin's, Chlo: Chloramphenicol, Est: Streptomycin, SPECT/CT scan: Three-phase bone SPECT/CT scan, PneumoEnc: Pneumoencephalogram, AngCarot: Carotid angiogram, HIC: Immunohistochemistry, TMP: Temporomandibular joint disorders, OP: Orthopantomography, MRI: Magnetic resonance imaging, PET: Positron emission tomography, FDG: Fluorodeoxyglucose. * Cervical lymph node and upper pharynx biopsy. Transcranial biopsy of the clival region by neuroendoscopy. ** Patient who was wrongly diagnosed with initial craniofacial fibrous dysplasia.

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] 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.[7] 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 sings 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[3,21,23] 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.

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Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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