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Frontal cutaneous and bone sarcoidosis: an example of the contiguous spread of granulomas

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Abstract. Sarcoidosis is a multisystemic granulomatous disease of unknown origin. It has been argued that the skin is one of the entry doors of the possible antigen that causes sarcoidosis and after entering the skin, the causal agent may progress to the underlying bone. We report four cases with development of sarcoidosis in old scars located on the forehead, and contiguous bone involvement of the frontal bone. In most cases scar sarcoidosis was the first manifestation of the disease, and in most cases it was asymptomatic. Two patients never required treatment, and in all cases the frontal problem improved or remained stable spontaneously or under sarcoidosis treatment. Scar sarcoidosis in the frontal area may have contiguous bone damage. This bone involvement does not seem to be associated with neurological extension.

Key words: Sarcoidosis, scar sarcoidosis, cutaneous involvement, bone involvement, musculoskeletal-cutaneous involvement

Background

Sarcoidosis is a systemic disease of unknown etiology, characterized by the formation of granulomas, whose incidence varies according to gender, age, race, and geographical region (1).

The lung and intrathoracic lymph nodes are concerned in more than 90% of cases, with other sites also commonly affected, such as extrathoracic lymph nodes, skin, and eyes (2). The occurrence of cutaneous involvement in scarred areas, whether due to factors such as physical trauma, surgery, tattoos, or burns, is a distinctive manifestation of sarcoidosis (3). Bone is less frequently affected (~3-30%) (4), and some authors report that it is infrequent in the absence of skin involvement (5,6). A study based on a large European sarcoidosis cohort, recognized a cluster of patients with predominant musculoskeletal-cutaneous involvement (6). However, the mechanisms of this association are not fully understood.

We report four cases with development of sarcoidosis in old scars located on the forehead, and contiguous bone involvement of the frontal bone (Table 1).

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Table 1. Patients' characteristics

Case	1	2	3	4
Gender	Male	Male	Male	Female
Age at sarcoidosis diagnosis	28 years	22 years	61 years	45 years
Race/ Country of origin	Caucasian/ France	Caucasian/ Algeria	Caucasian/ Portugal	Black/ Comoro Islands
Smoking history	No	No	No	No
Cause of the scar	Trauma	Unknown	Trauma	Trauma
Time between sarcoidosis diagnosis and appearance of cutaneous lesion	Concomitant	26 months	Concomitant	Concomitant
Frontal lesion symptoms	Asymptomatic	Asymptomatic	Asymptomatic	Pain
Scadding staging	I	I	II	I
Systemic involvement of sarcoidosis	Cutaneous, bone	Cutaneous, bone, ocular, lymph nodes, nasosinusal	Lymph nodes, cutaneous, bone	Ocular, cutaneous, bone, lymph nodes, neurological, parotid gland
Biology				
SACE (normal < 70U/L)	83 U/L	96 U/L	50 U/L	99 U/L
Calcium level	Normal	Normal	Normal	Normal
Serum protein electrophoresis	Normal	Normal	Normal	Normal
MRI findings:				
Frontal subcutaneous nodule:				
- size	10 mm	10 mm	10.7 mm	10 mm
- gadolinium enhancement	No	Yes	Yes	Yes
- contact with the bone lesion	Yes	Yes	Yes	No
Frontal bone lesion:				
- size	<5 mm	9 mm	10.8mm	10 mm
- gadolinium enhancement	No	Yes	Yes	Yes
- lytic aspect	No	Yes	Yes	Yes
- scalloping of the outer tabula	Yes	Yes	Yes	Yes
- scalloping of the inner tabula	No	No	Yes	No
- diploe invasion	No	No	Yes	Yes
18 FDG PET scan uptake				
Frontal subcutaneous nodule	N/A	N/A	Yes: SUVmax 4.5	Yes: SUVmax 15.2
Frontal bone lesion			Yes: SUVmax 4.5	Yes: SUVmax 7.4
Treatment	No	Hydroxychloroquine, steroids	No	Steroids, Methotrexate, Infliximab
Evolution				18 months
Duration of follow-up	78 months	117 months	53 months	Reduction on MRI
Frontal subcutaneous nodule	Stability on MRI	Regression on MRI	Reduction on MRI	Marked decrease in PET
Frontal bone lesion	Stability on MRI	Reduction on CT	Reduction on MRI	uptake

Abbreviations: MRI: magnetic resonance imaging; PET: positron emission tomography, CT: computed tomography

Clinical cases

Case 1

A 28-year-old Caucasian male, with a history of football accident that left him with a scar on his forehead, went to a plastic surgery consultation in January 2008 because of the growth of a painless subcutaneous nodule at the site of the trauma. The lesion was excised and pathological analysis revealed non-caseous epithelioid granulomas. The patient was in good general condition and he only complained of dry cough. Chest computed tomography (CT) showed isolated enlargement of hilar lymph nodes, and pulmonary function tests (PFTs) were normal. ^{99m}Technetium bone scintigraphy showed tracer uptake in the T12 vertebra and under the frontal subcutaneous lesion. Head magnetic resonance imaging (MRI) revealed bone lysis in the latter region without neurological involvement. Cough resolved with inhaled steroids, and the patient never needed systemic treatment during follow-up.

Subsequent control MRI scans showed spontaneous disappearance of the T12 lesion and stability of the frontal bone lesion in May 2014.

Case 2

A 22-year-old Caucasian male was diagnosed with sarcoidosis in January 2008, including radiographic stage I, skin involvement and anterior uveitis. He was treated with hydroxychloroquine, which was inefficient and stopped in January 2009. In March 2010, sarcoidosis progressed, with weight loss, fatigue and development of nasal symptoms and conjunctiva nodules. A painless nodular subcutaneous lesion appeared in the frontal region on an old scar. Biopsy of the lesion and cervical lymph node revealed non-caseous epithelioid granulomas. Head-CT showed osteolysis of the frontal bone under the subcutaneous nodule. Head-MRI confirmed this bone involvement, without neurological involvement. [18] FDG Positron Emission Tomography (PET) scan did not cover the frontal region but revealed hypermetabolic cervico-abdominopelvic lymphadenopathy and multiple bone foci (scapular, vertebral, pelvic). The patient received steroids from January 2011 to July 2013. There was a clear improvement in symptoms and no recurrence until February 2020 where new skin localizations developed on the knees, back and elbows. Repeated head-CT showed significant reduction in the frontal bone lesion and head-MRI showed regression of the subcutaneous nodule. The patient remained untreated as skin lesions were not cosmetically troublesome.

Case 3

This 61-year-old Caucasian male, with no relevant medical history, had a car accident with trauma to the forehead around 15 years ago, which left a scar and a tumefaction at this site that receded spontaneously. In January 2018, he went to a consultation for reappearance of the tumefaction without pain. Head-CT scan demonstrated frontal bone lysis. Head-MRI evidenced a medial frontal subcutaneous nodule in contact with the bone lesion that showed focal lysis of the external plate and no neurological involvement. PET scan demonstrated, besides an increased uptake of the frontal bone lesion and adjacent subcutaneous nodule, hypermetabolic mediastinal-hilar lymphadenopathy, as well as perilymphatic micronodular lung infiltrates. A mediastinoscopy was performed in March 2018 revealing non-caseous epithelioid granulomas. The patient was referred to our department in May 2020 where a surgical biopsy of the bone lesion was discussed but considered too risky. The biopsy of a new skin lesion on the tip of the nose also confirmed the presence of granulomas. As the patient was asymptomatic and PFTs were normal, he was not treated. In the most recent control head-MRI in June 2022 there was a reduction in the size of the frontal lesion.

Case 4

A 45-year-old black female was hospitalized in October 2020 for dysphagia and dysphonia, which was related to a right vocal cord paralysis, and non-systematized diffuse neuropathic pain. Physical examination revealed a left pre-auricular lymph node with non-caseous epithelioid granulomas on biopsy. There was also evidence of a painful subcutaneous nodule on the forehead on an old scar that was caused by injury during a boxing match several years ago. Frontal nodule biopsy confirmed localization of sarcoidosis. Chest CT showed isolated mediastinal-hilar lymphadenopathy. Steroids were started with improvement in all except neurological symptoms. In April 2021, PET scan evidenced increased uptake in lymphadenopathy, left frontal lesion (Figure 1) and cauda equina confirmed by spinal MRI. Head-MRI confirmed the subcutaneous and external plate involvement of the frontal bone and no encephalic involvement (Figure 1). The patient

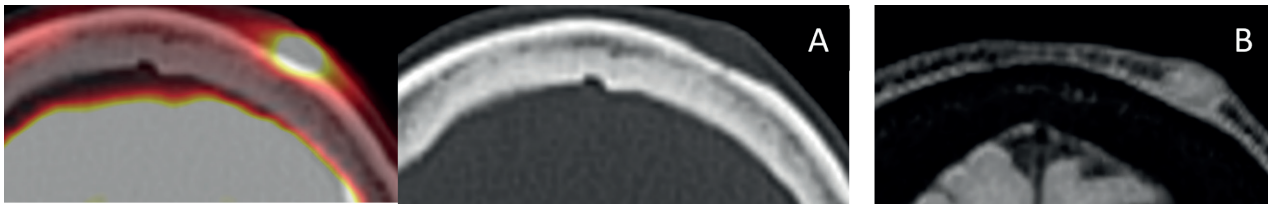

Figure 1: A) (PET CT 2022): subcutaneous FDG avid nodule with scalloping of the external tabula without invasion of the diploe. B) (MRI 2022, T1WI Fat Saturated with contrast): nodule homogeneously enhanced

was treated with methotrexate and from December 2021 with infliximab allowing normalization of spinal MRI. At last visit in June 2022, she still had some pain on the forehead. Head-MRI showed stability in bone lesion and partial regression of the subcutaneous nodule, and uptake has improved at PET scan.

Discussion

In all our cases there was subcutaneous development of sarcoidosis on old scars, and frontal bone involvement was found under the lesion. In three patients the scars were due to trauma. Also, in three patients, scar sarcoidosis was the first manifestation of the disease.

Bone involvement is uncommon in sarcoidosis, but underdiagnosed since it is often asymptomatic, as in three of our cases where it was merely discovered during the imaging investigation of the subcutaneous lesion. Currently, with the advent of PET scan, there is a greater diagnosis of bone involvement, often accidental (4).

Sarcoidosis bone involvement is frequently accompanied by skin involvement (5,6,7). It has been argued that the skin is one of the entry doors of the possible antigen that causes sarcoidosis. Colboc et al. identified inorganic deposits inside cutaneous granulomas (8). Beijer et al. confirmed the presence of *P. acnes* in tissues (skin, bone, and others) and granulomas of Dutch sarcoidosis patients, also hypothesizing an organic source (9). After entering the skin, the causal agent may progress to the underlying bone (10).

Interestingly, in the study by Bae et al. focusing on scar sarcoidosis, regional predilection was found in the head and neck (11). The contiguous spread of the granulomatous process from the forehead skin to the frontal bone seen in our cases may be favored by the particularly thin soft tissue in this anatomical zone. Noticeably, one patient had cauda equina involvement but no leptomeningeal enhancement at encephalic level. In keeping with several studies on sarcoidosis bone involvement, hypercalcemia was not observed in our patients (5).

None of our patients underwent confirmatory biopsy of the frontal bone lesion, which was assumed to be a localization of sarcoidosis. In all patients the main differential diagnoses of such bone lesion were excluded, namely tuberculosis, metastatic disease and multiple myeloma, and its evolution was suggestive of sarcoidosis. In fact, two patients never required treatment, and in all cases the frontal problem improved or remained stable spontaneously or under sarcoidosis treatment.

Conclusion

Scar sarcoidosis in the frontal area may have contiguous bone damage. This bone involvement, often indolent, does not seem to be associated with neurological extension.

Conflict of Interest: The authors declare to have no conflict of interest directly or indirectly related to the manuscript contents.

Institution where work was done: Avicenne Hospital (Assistance Publique – Hôpitaux de Paris), Bobigny, Paris, France.

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