ORIGINAL ARTICLE

Imaging in sinonasal sarcoidosis: CT, MRI, 67Gallium scintigraphy and 18F-FDG PET/CT features

Imagerie par TDM, IRM, scintigraphie au 67Gallium et TEP TDM au 18F-FDG dans la sarcoïdose nasosinusienne

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KEYWORDS
Sinonasal sarcoidosis; Sarcoidosis; CT; MRI; 67Gallium scintigraphy; 18F-FDG positron emission tomography; Granulomatous disease

Summary
Objectives. — Attempt to describe and analyse the radiological and nuclear medicine patterns of sinonasal sarcoidosis (SNS) still poorly reported in the literature.

Material and methods. — Retrospective single institution study of 22 consecutive patients with symptomatic biopsy-proven SNS to evaluate the interest of CT, MRI, 67Ga scintigraphy and 18F-FDG PET/CT for diagnosis and therapeutic follow-up.

Results. — Nodules of the septum and turbinates are the most suggestive CT and MRI features. Other CT features such as sinus filling, mucosal thickening, osteosclerosis or destructive sinonasal lesions are not specific and depend on clinical context and evolutive stage of SNS. 18F-FDG PET/CT provides complete morphofunctional mapping of active inflammatory sites related to sarcoidosis with a better diagnostic sensitivity (100%) compared to 67Gallium scintigraphy (75%). The changes in 18F-FDG uptake intensity could reflect the efficacy of treatment.

Conclusion. — SNS is an uncommon and probably underdiagnosed phenotype of sarcoidosis. Even if guided biopsy remains necessary for SNS confirmation, medical imaging plays an important role in diagnosis and therapeutic follow-up. CT features with nodules of the septum and/or turbinates are suggestive of SNS contrary to other nonspecific CT findings. CT imaging is directly related severity, reversibility and course of SNS and provide an original radiological staging system in order to predict patient clinical outcome. PET/CT may be used for diagnosis assessment but also to monitor treatment response in a given clinical context, in a patient with histopathologically-proven SNS. Prospective and long term studies are necessary to validate these preliminary results.

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Introduction

Sarcoidosis is a chronic noncaseating granulomatous disease of unknown origin, principally affecting the respiratory tract [1–3]. Granulomatous involvement of sinonasal mucosa, already described by Boeck in 1905, is rare and has been estimated at between 0.7% and 6% [3–5]. Sinonasal sarcoidosis (SNS) can be part of multisystemic sarcoidosis or more exceptionally can be isolated. The clinical presentation is protean and nonspecific and SNS diagnosis remains difficult [1–12]. The natural history, course and prognosis of SNS are poorly understood and unpredictable [3,4]. SNS is associated with a severe local and general phenotype of sarcoidosis [2–4,7,11]. The treatment has not yet been standardized and the long-term therapeutic results remain globally disappointing despite high doses of systemic corticosteroids and/or immunosuppressive drugs [2–4,6–8]. Medical imaging plays an important role in diagnosis and therapeutic management of patients with SNS [1–3,5,7,8,10–20].

Based on a retrospective analysis of CT, MRI, 67Ga scintigraphy and 18F-FDG PET/CT features obtained from 22 consecutive patients with symptomatic and biopsy-proven SNS, the aim of our study was to evaluate the usefulness of morphofunctional approach in SNS management, analyzing the radiological and scintigraphic imaging patterns of SNS, still poorly reported in the literature.

Materials and methods

Patient population

Between 1994 and 2008, 22 consecutive patients with symptomatic biopsy-proven SNS were retrospectively selected for this study. The patient population included 12 males and 10 females: 11 Europeans, six North Africans and five Africans. Their age ranged from 41 to 79 years with a mean age of 50 years.

Patients underwent a standard evaluation including:

- history and physical examination, with particular attention paid to the upper and lower respiratory tract;
- endoscopic evaluation of the nasal cavities, pharynx, larynx, and bronchi;
- high-resolution sinonasal CT in all cases;
- chest radiological evaluation, including standard radiography and/or high-resolution CT;
- pulmonary function tests with assessment of single-breath diffusing capacity of the lung for carbon monoxide;
- biological evaluation, including measurement of serum angiotensin-converting enzyme, antineutrophil cytoplasmic antibodies;
- multiple biopsies of visible and accessible granulomatous lesions with histopathological confirmation of sarcoidosis in all cases;
- other investigations for differential diagnosis purposes.

Patients underwent MRI, 67Ga scintigraphy and 18F-FDG PET/CT at primary staging and/or during therapeutic follow-up. The selection criteria for these patients with more than one imaging modality were: atypical clinical presentation, suspicion of multisystemic sarcoidosis, difficulties in evaluation of SNS during and after treatment (relapse, poor response to corticosteroids), evaluation of the clinical impact of imaging without using systematically all imaging technics for each patient for economical and ethical (irradiation) reasons.

All images were retrospectively interpreted, blindly and separately, by experienced radiologists and nuclear medicine physician which were uninformed about clinical findings and topography of sarcoidosis lesions detected by the conventional diagnostic approach.

Imaging technical features

CT

The sinonasal system was imaged with CT in spiral axial planes parallel to the hard palate. An Elscint CT (Israel) was used between 1994 and 2000. The institution’s routine high-resolution protocol was applied. The acquisition parameters were 120 kV, 150 mAs, and 1.1-mm beam collimation. The reconstruction parameters were 1.1-mm section thickness with a 0.6-mm increment, 15-cm FOV, and a high-resolution kernel (U 80u).

After 2000, a 16-detector row Multi-Detector CT Imager (MDCT) (Somaris, Siemens Medical Systems, Erlangen, Germany) was employed. The acquisition parameters were 120 kV, 150 mAs, and 0.6-mm beam collimation. The reconstruction parameters were 0.6-mm section thickness with a 0.3-mm increment, 15-cm FOV, and a high-resolution kernel (U 80u). Reconstructed images were realigned along parallel and perpendicular planes to the hard palate in order to obtain both sagittal and coronal slices.

The CT images were viewed using the large window (width/level, W/L) bone technique (4000/700, W/L) and with the soft-tissue window setting (350/40) with a standard kernel (U 30u).

All CT examinations were performed with no contrast media injection.

MRI

MRI investigations were performed on a 1.5-Tesla MR unit (AVANTO, Siemens Medical Systems, Erlanger, Germany), using the following protocols:

- T2-weighted axial turbo spin echo (20 slides, gap: 0.9 mm, matrix: 384 x 384, voxel size: 0.6 x 0.6 x 3 mm, TR = 3080 ms, TE = 107 ms, two excitations, FOV 230);
- T2-weighted coronal turbo spin echo (20 slides, gap: 0.9 mm, matrix: 384 x 259, voxel size: 0.69 x 0.63 x 3 mm, TR = 3290 ms, TE = 107 ms, two excitations, FOV 240).
- T1-weighted axial spin echo (20 slides, gap: 0.9 mm, matrix: 384 × 286, voxel size: 0.64 × 0.57 × 3 mm, TR = 500 ms, TE = 12 ms, two excitations, FOV 220);
- T1-weighted axial spin-echo water excitation with gadolinium injection (Gadoteric Acid, Dotarem®, 0.2 ml/kg) (20 slides, gap: 0.9 mm, matrix: 286 × 384, voxel size: 0.64 × 0.57 × 3 mm, TR = 12 ms, two excitations, FOV 220);
- T1-weighted coronal spin-echo water excitation with gadolinium injection (20 slides, gap: 0.9 mm, matrix: 320 × 320, voxel size: 0.63 × 0.63 × 3 mm, TR = 565 ms, TE = 12 ms, one average, FOV 200).

67Ga scintigraphy
Five selected patients underwent 67Ga scintigraphy 72 h after intravenous injection of 185 MBq of 67Ga-citrate (67Ga-citrate, CIS Bio International, France). To avoid enterohepatic circulation of radiotracer resulting in intestinal background, a mild laxative was given beginning 2 days before the first day of image acquisitions. WB planar imaging and single photon emission tomography (SPECT) acquisitions were performed with a large-field-of-view two-head gamma camera (ECAM, Siemens Medical Systems, Erlangen, Germany) equipped with medium-energy collimators and 20% energy windows centered at 93, 185 and 300 keV. Anterior and posterior WB planar images (matrix, 256 × 1024) were acquired at a speed of 12 cm/min. Thorax and abdominopelvic SPECT (WB SPECT), consisting in 2-FOV SPECT, were systematically done. A single FOV SPECT study was performed by 360° arc step-and-shoot acquisition, 32 projections and 64 × 64 matrix. Data were acquired 45 s per projection, for a total imaging time of 28 min. Transaxial, sagittal and coronal images were reconstructed from projection data with the Ordered Subset Expectation Maximization (OSEM) iterative algorithm (four iterations, four subsets) and qualitatively interpreted.

18F-FDG PET/CT
A combined PET/CT scanner was employed for all patients examined (Discovery ST, GE Medical Systems, Milwaukee, WI, USA). To obtain a serum glucose level less than 6.6 mmol/L, the patient fasted for 6 h before the intravenous injection of 5.5 MBq/kg of 18F-FDG (Flucis, CIS Bio International, France). Five milligrams of diazepam and 80 mg of phloroglucinol (musculotropic antispasmodic) were previously administered to the patient. Whole-body (WB) PET/CT acquisitions started 60 min after tracer injection, including a head-to-mid thigh no contrast-enhanced CT scan (140 KV, 80 mAs, 0.8 s/rotation) during current breathing, followed by a two-dimensional PET scan (seven fields of view, 15 cm/field, 4 min/field, 3.27-mm slice thickness). PET data were reconstructed with and without CT-based attenuation correction using the OSEM iterative algorithm (two iterations, 15 subsets, 128 × 128 matrix). CT, PET (corrected), and combined PET/CT images were displayed on an Xeleris work station (GE Medical Systems, USA) and visually interpreted. For quantitative analysis of 18F-FDG uptake, the maximum standardized uptake value (mSUV) per focus was used. Those values were then considered for residual inflammatory activity assessment.

Results
Clinical presentation and endoscopic results
The mean delay between the early sinonasal symptoms and the histopathological confirmation of SNS was 5 years (range, 2–10 years) for 18 cases. It could not be determined in the four remaining patients. The most frequent clinical presentation of SNS was chronic inflammatory rhinitis or rhinosinusitis that was sometimes crusty and rarely destructive with modifications of the nasal pyramid (Fig. 1), especially in patients with delayed diagnosis and/or relapsing or progressing disease despite treatment.

Figure 1  Modifications of the morphological aspect of the nose in a patient with SNS. (a) A 40-year-old man: recovery from SNS with no modification of the nasal pyramid after 8 years of CS treatment. (b) Same patient 2 years later after withdrawal of CS treatment: relapse of SNS with substantial modification of nasal pyramid.
Radiological and nuclear medicine imaging in sinonasal sarcoidosis

Table 1  Main clinical symptoms of SNS.

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal obstruction, stuffiness</td>
<td>18</td>
</tr>
<tr>
<td>Anterior or posterior rhinorrhea</td>
<td>16</td>
</tr>
<tr>
<td>Nasal crusting</td>
<td>9</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>9</td>
</tr>
<tr>
<td>Facial pain</td>
<td>5</td>
</tr>
<tr>
<td>Anosmia</td>
<td>9</td>
</tr>
<tr>
<td>Dysphagia and/or dyspnea</td>
<td>2</td>
</tr>
<tr>
<td>Other symptoms of skin, salivary and lacrimal glands, orbit, cervical lymph node involvement</td>
<td>17</td>
</tr>
</tbody>
</table>

The patients’ main clinical symptoms are summarized in Table 1.

In 17 cases, a careful ear, nose and throat endoscopic examination showed small, often pale, yellowish or sometimes erythematous nodules or granulations (3–5 mm in diameter) of the turbinates and/or the septum (Fig. 2a). Sometimes these nodules were confluent in large granulations covered with crusts in some cases (Fig. 2b). Sarcoidosis involvement of the nasal mucosa was proven by guided biopsy in all patients (Fig. 2c). Other endoscopic features such as inflammatory mucosa, nasal synechia, lysis or thickening of the septum and polyps of the middle meatus were not specific and depended on the clinical context.

The ENT endoscopic features are summarized in Table 2.

Table 2  ENT examination features.

<table>
<thead>
<tr>
<th>ENT examination features</th>
<th>n = 22</th>
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</thead>
<tbody>
<tr>
<td>Nodules of turbinates and/or septum</td>
<td>17</td>
</tr>
<tr>
<td>Nasal crusting</td>
<td>10</td>
</tr>
<tr>
<td>Inflammatory nasal mucosa</td>
<td>15</td>
</tr>
<tr>
<td>Nasal synechia</td>
<td>5</td>
</tr>
<tr>
<td>Thickening or lysis of the septum</td>
<td>6</td>
</tr>
<tr>
<td>Polyps of the middle meatus</td>
<td>3</td>
</tr>
<tr>
<td>Modifications of the nasal pyramid</td>
<td>4</td>
</tr>
<tr>
<td>Soft nasal tissue involvement</td>
<td>2</td>
</tr>
<tr>
<td>Sinusal mucosa involvement (sinoscopy, surgery)</td>
<td>3</td>
</tr>
<tr>
<td>Involvement of the pharynx and/or larynx</td>
<td>7</td>
</tr>
<tr>
<td>Facial cutaneous involvement (lupus pernio, nodules, scars)</td>
<td>10</td>
</tr>
<tr>
<td>Ophthalmic involvement</td>
<td>5</td>
</tr>
<tr>
<td>Salivary gland involvement</td>
<td>6</td>
</tr>
<tr>
<td>Cervical lymphadenopathies</td>
<td>3</td>
</tr>
</tbody>
</table>

Histopathological and biological findings

At least one or several biopsies were done for each patient and integrated in the clinical context to confirm sinonasal sarcoidosis involvement. Biopsies of the skin, bronchi, accessible lymph nodes, liver, stomach, pharynx and larynx were also done in case of associated sarcoidosis locations in multisystemic disease.

Sarcoidosis was histopathologically proven by the presence of noncaseating epithelioid giant-cell granulomas on biopsy samples (Fig. 2c). Histopathological examination was negative for fungus, acid-fast bacilli and for other diseases such as vasculitis or neoplasia.

In 15 patients, the level of serum angiotensin-converting enzyme was pathologically increased and normal in five cases. Investigations for antineutrophil cytoplasmic antibodies and mycobacteria were negative in all patients.

CT findings

Nodules of the turbinates (12 cases) and septum (17 cases) were the most commonly encountered radiological finding in SNS with sometimes mucosal synechia (Fig. 3a). An experienced analysis of the images was necessary to detect nodules or granulations, which could be easily overlooked. In some cases, the nodules were confluent with a CT aspect of corrugated iron, especially in the septum and/or turbinates (Fig. 3b). The axial planes were the most informative views to demonstrate the nodules on turbinates and septum (Fig. 3). Other CT features such as sinus filling, mucosal thickening or destructive bony and/or cartilaginous sinonasal lesions were not specific and depended both on clinical context and evolutive stage of disease (Figs. 4 and 5). No imaging of fluid retention was observed in any of the cases of SNS. Five patients did not display the suggestive nodular findings of SNS on CT. So the clinical impact for diagnosis of SNS can be estimated for CT imaging (visible nodules) about 77% in this series.

Figure 2  Endoscopic views of the nasal cavities and microscopic examination in SNS. (a) Mucosal nodules (arrows). (b) Crusting nasal mucosa. (c) Microscopic examination (H&E, × 100) of nasal biopsy: non-necrotizing epithelioid giant-cell granulomas (courtesy of G. Averous, MD).
Figure 3  Non-contrast-enhanced CT axial slices of a patient with SNS. (a) A 41-year-old woman: multiple nodules of septum and inferior turbinates associated with left maxillary sinus filling. (b) Same patient 2 years later: confluent nodules of septum and inferior turbinates with a corrugated iron aspect. Postsurgical sequelae of the left maxillary sinus.

Figure 4  Modifications of nasal pyramid in a patient with SNS. (a) A 30-year-old man: normal nasal morphology. (b) Same patient 15 years later with SNS: substantial modification of nasal pyramid.

Figure 5  Non-contrast-enhanced CT axial slices in a case of advanced SNS in a 45-year-old patient (same patient as in Fig. 4b). (a) Lysis of inferior turbinates, osteosclerosis of the maxillary sinusual walls, involvement of nasal tip and mucosal thickening of maxillary sinuses. (b) Lysis of the septum, ethmoidal clefts, planum bone of the ethmoid and nasal bones. Ethmoidal and left sphenoidal sinus filling.
Table 3  CT features of SNS.

<table>
<thead>
<tr>
<th>CT features</th>
<th>n = 22</th>
</tr>
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<tbody>
<tr>
<td>Sinonasal lesions</td>
<td>22</td>
</tr>
<tr>
<td>Nodules on septum</td>
<td>17</td>
</tr>
<tr>
<td>Nodules on turbinates</td>
<td>12</td>
</tr>
<tr>
<td>Mucosal hyperplasia and sinus filling</td>
<td>17</td>
</tr>
<tr>
<td>Involvement of the ostiomeatal complex</td>
<td>4</td>
</tr>
<tr>
<td>Filling of the olfactory cleft</td>
<td>4</td>
</tr>
<tr>
<td>Nasal mucosa synchia</td>
<td>4</td>
</tr>
<tr>
<td>Septal thickening or lysis</td>
<td>6</td>
</tr>
<tr>
<td>Lysis of the turbinates</td>
<td>4</td>
</tr>
<tr>
<td>Lysis of the ethmoidal walls and clefts</td>
<td>5</td>
</tr>
<tr>
<td>Lysis of the nasal bones</td>
<td>4</td>
</tr>
<tr>
<td>Lysis of the hard palate</td>
<td>1</td>
</tr>
<tr>
<td>Nasal soft tissue involvement (skin, tip of the nose)</td>
<td>3</td>
</tr>
<tr>
<td>Osteosclerosis of sinusal walls</td>
<td>5</td>
</tr>
<tr>
<td>Rhinopharynx involvement</td>
<td>4</td>
</tr>
<tr>
<td>Orbital involvement (exophthalmia, perineuritis, lacrimal glands)</td>
<td>7</td>
</tr>
<tr>
<td>Salivary gland involvement</td>
<td>4</td>
</tr>
</tbody>
</table>

The overall CT results are summarized in Table 3.

MRI findings

MRI imaging was performed in three patients and compared to CT evaluation. The main MRI features were (Fig. 6a, b):

- nodules on septum and inferior turbinates in all three cases;
- septal mucosal thickening and lysis of the septum in one case;
- mucosal thickening of maxillary sinuses in two cases, filling of ethmoidal sinuses in two cases and frontal sinus in one case;
- involvement of the nasal tip or of the paranasal soft tissues in two cases.

These MRI imaging patterns correlated well with the endoscopic and CT results.

Other CT and MRI ENT-findings associated with SNS

CT and MRI showed the following head and neck sarcoidosis locations associated with SNS (Table 3):

- rhinopharynx in four patients with a pseudotumoral aspect in two cases;
- ophthalmic involvement, in particular the lacrimal glands, ophthalmic nerve, orbital plate of the ethmoid and exophthalmia in seven patients;
- salivary gland involvement in four cases.

67Gallium scintigraphy features

Five patients underwent 67Ga WB planar and SPECT scintigraphy. Four patients showed a clinical symptomatology suggesting relapse or persistence of active granulomatous disease. The fifth patient in clinical remission underwent a scintigraphy after corticosteroid therapy.

A pathological uptake of radiotracer was detected in the sinonasal region in only three of four patients with active disease (Fig. 7c, d, e). No clear simultaneous involvement of parotid and lacrimal glands (panda sign) was shown. A true-negative result was obtained in the sole patient achieving clinical remission.

Even if the use of multiple-head gamma cameras with SPECT capability has improved image resolution of smaller lesions, no real difference in terms of sensitivity was detected between 67Ga planar imaging and 67Ga SPECT.

18F-FDG PET/CT findings

18F-FDG PET/CT was performed in seven of the 22 SNS and in three cases of chronic rhinosinusitis mimicking SNS (Table 4). Five out of seven showed endoscopic and radiological signs of active SNS. The remaining two patients were in clinical remission.

Figure 6  Contrast-enhanced fat-suppressed T1-weighted MRI in a patient with SNS. (a) A 35-year-old woman in early-stage disease (axial view): multiple nodules of septum and inferior turbinates, inflammatory mucosal hyperplasia of right maxillary sinus, left maxillary sinus mucosal cyst. (b) Same patient 18 months after stopping CS treatment (coronal view): disease recurrence with substantial thickening of septum and sarcoidosis involvement of septal cartilage and right paranasal tissues.
Figure 7  Scintigraphic results in a 42-year-old patient with SNS in multisystemic sarcoidosis. 18F-FDG PET lateral (a) and anterior (b) view of whole-body maximum intensity projection (MIP), 67Ga scintigraphy anterior WB (c) anterior (d) and lateral (e) planar spot of head and neck. Intense pathological radiotracer uptake was shown in sinonasal regions in both PET and scintigraphy. Discordance between PET images, showing multiple foci of pathological uptake and 67Ga scintigraphy was shown in assessment of extrasinonasal involvement.

All biopsy-proven SNS locations were characterized by intense glucose metabolism related to active inflammatory disease (Figs. 7a, b, 8a, b, 9a). Moreover, 18F-FDG PET/CT highlighted multiple foci of pathological tracer uptake in the thorax (five patients), pharynx and larynx (four patients), abdomen and pelvis (three patients) and peripheral lymph nodes, bone, muscle and spleen (nine patients), suggesting multisystemic sarcoidosis, which had not always been previously detected by conventional evaluation (Fig. 7a, b). No pathological 18F-FDG uptake was shown in the two patients with no evidence of active SNS.

Comparatively to these seven cases with biopsy-proven SNS, PET/CT was performed in three cases of chronic rhinosinusitis with a clinical presentation mimicking SNS but without proven-SNS by biopsy. In these three cases PET/CT showed no pathological tracer uptake sinonasal foci.

To evaluate 18F-FDG PET/CT potential in SNS follow-up, four patients underwent a second scintigraphic exploration to access therapeutical response, remembering that biopsy is not helpful in patients with corticosteroidtherapy. The PET/CT results were compared to conventional evaluation and to the first PET/CT evaluation. One patient with SNS within systemic sarcoidosis underwent follow-up PET/CT 19 months after the first examination. During this period he received 40 mg of prednisolone per day, progressively reduced to 15 mg/day, showing a good clinical and endoscopic response. Despite great improvement in scintigraphic abnormalities, persistence of residual 18F-FDG uptake in the sinonasal region was shown (Fig. 9a, b). Treatment failure with evidence of active disease was assessed in one patient who underwent a second scintigraphic evaluation after 16 months of decreasing doses of prednisolone (from 40 to 2 mg/day). Disease recurrence was assessed in two patients with clinical suspicion of relapse 16 and 18 months after withdrawal of CS (Fig. 10a, b).

Endoscopic evaluation and sinonasal CT findings correlated well with the PET/CT results.

Overall imaging results for evaluation of SNS

According to the suggestive imaging patterns of SNS, the clinical diagnostic impact of imaging can be evaluated with possible bias especially for the imaging technics used in only few cases:

- CT (visible nodules): 77% for all 22 cases;
- MRI (visible nodules): 100% for three cases;
- 67Ga Scintigraphy (sinonasal tracer uptake): 75% for five cases;
Figure 8  Axial CT, attenuation-corrected $^{18}$F-FDG PET and PET/CT fused images in two patients with SNS (42 and 78 years old). Pathological uptake of radiotracer was shown in (a) septal cartilage and bilateral paranasal tissues and in (b) septum and turbinates, corresponding to CT abnormalities.

- $^{18}$F-FDG PET/CT (sinonasal tracer uptake): 100% for seven cases by inclusion evaluation and four cases by therapeutic evaluation and no tracer uptake in three cases of chronic rhinosinusitis without proven-SNS.

According to clinical symptomatology and results of the endoscopic and radiological evaluation and biopsy, the study population could be divided into two different groups:

- isolated SNS (two patients);
- SNS in multisystemic sarcoidosis (20 patients).

Figure 9  Sagittal CT, attenuation-corrected $^{18}$F-FDG PET and PET/CT fused images in 45-year-old man with SNS in multisystemic sarcoidosis at primary staging (a) and after CS treatment (b). Despite the persistence of slight scintigraphic abnormalities in sinonasal cavities, note the great improvement in glucose hypermetabolism described at first PET/CT.

Figure 10  Axial CT and attenuation-corrected $^{18}$F-FDG PET images in a 37-year-old patient with SNS in primary staging (a) and 16 months after CS withdrawal (b). Pathological uptake on septum and turbinates suggested disease recurrence which was endoscopically confirmed.

Discussion

Compared to well-known mediastinal thoracic sarcoidosis, the radiological and scintigraphic pattern of SNS has not been thoroughly and specifically analyzed in large series of patients in the literature [3,4–6,12,13–18].

CT plays an important role in management of this disease. Nodules and granulations of the nasal septum or the turbinates, which are often visible only after experienced analysis, are suggestive of SNS and must lead to guided nasal biopsy. Sinusal filling and mucosal thickening, in particular of the maxillary sinuses and anterior ethmoid, osteosclerosis of the sinusal walls, bony or cartilaginous
sinonasal destructions can be encountered in SNS but also in other chronic rhinosinusitis, nasal polyposis, and granulomatous diseases such as Wegener syndrome and in postsurgical sequelae [1,3,5,12,14,18]. No fluid retention was visible on CT. Therefore diagnosis of SNS cannot be based on CT findings alone but needs biopsy confirmation after withdrawal of any corticosteroid treatment.

In three patients, MRI showed the same imaging pattern as CT, adding no useful complementary information (Fig. 6). MRI seems more interesting for evaluation of ophthalmic sarcoidosis and/or neurosarcoidosis according to the literature data [12].

The analysis of serial CT examinations performed in all cases as well as clinical, endoscopic, biological and follow-up evaluation allowed us to evaluate the course of SNS. The follow-up period including all patients ranged from 1 to 15 years (mean, 6 years). For biopsy proven SNS, nasal nodular CT images which are often associated with sinonasal mucosal thickening, characterize the early stage of SNS. On the other hand, involvement of cartilagenous and bone sinonasal structures, with lytic and/or osteosclerotic images and sometimes infiltration of the tip of the nose or paranasal soft tissues, are suggestive of advanced stages of the disease. The osteocartilaginous modifications are principally found in aggressive SNS forms as well as in cases of delayed diagnosis and therapeutic failure or recurrency after withdrawal or decreasing doses of corticosteroids (Figs. 1b, 3b, 4b, 5a, b, 6b, 9b, 10b). In our experience, CT and MRI data correlated well with clinical, endoscopic, biological and biopsy evaluation and with SNS evolution (Figs. 4–6).

The CT features described herein, which were directly related to SNS severity, reversibility and course or progression of SNS within a long follow-up period, provide an original radiological staging system for SNS in order to predict patient clinical outcome:

- stage I: limited and superficial nasal mucosa involvement with or without variable sinonasal mucosal thickening or filling of the sinuses (Figs. 3a and 6a) corresponding to moderate and reversible SNS lesions;
- stage II: involvement of sinonasal mucosa, nasal or sinonasal bony and/or cartilagenous structures and nasal and paranasal soft tissues corresponding to severe and irreversible SNS lesions (Figs. 5 and 6b).

Comparatively to the staging system of Krespi in three stages based principally on clinical criteria [7] this radiological staging system could be used not only to describe the imaging patterns but also to guide the aggressiveness of treatment and to try to predict the prognosis (severity, reversibility, progression) of SNS in patient clinical outcome. These findings are supported by a long follow-up period during and after treatment for all patients. Prospective studies of biopsy-proven SNS with a complete endoscopic and radiological evaluation at inclusion assessment and a long follow-up are necessary to confirm these preliminary findings.

$^{18}F$-FDG PET/CT is a noninvasive imaging technique widely accepted in oncological routine. Neutrophils, macrophages and lymphocytes have increased $^{18}F$-FDG uptake, causing significant tracer accumulation in inflammatory processes. Slight $^{18}F$-FDG specificity seems to be a potential advantage in diagnostic work-up and follow-up of patients with inflammatory/infectious diseases such as fever of unknown origin and large-vessel vasculitis. Nevertheless, $^{18}F$-FDG PET capability for management of SNS has not been thoroughly evaluated [13–16,19,20]. Better imaging quality, fewer technical constraints and better sensitivity argue in favor of $^{18}F$-FDG PET compared to $^{67}$Ga scintigraphy [15,17]. Increased uptake of radiotracer is not specific of sarcoidosis. Therefore, a positive PET/CT result alone is not a diagnostic criterion of certainty for sarcoidosis nor an indication for treatment. Nevertheless, after achieving the histopathological demonstration of sarcoidosis, whole-body PET/CT allows complete morphofunctional mapping of active SNS and the frequently associated multisystemic sarcoidotic locations. In the population studied and in this investigation protocol, SNS was isolated in only two cases. PET/CT showed multiple extrasinonasal foci of pathological $^{18}F$-FDG uptake, suggesting multisystemic disease, which was often underestimated at conventional primary staging (Fig. 7 a, b). Were all these sites of pathological tracer uptake authentic, active, subclinical unknown sarcoidosis locations or were the lesions overestimated by PET/CT in some cases (false positive findings ?) [15,20]. As in other studies [15,16,20] unfortunately biopsy was not performed in all newly detected sites for technical and ethical reasons. So histopathological confirmation of sarcoidosis was obtained in only 30% of these sites in our series.

The changes in tracer uptake intensity could reflect the efficacy of medical treatment and could provide a better adaptation of drug dosage or a modification of the therapeutic strategy. In our study, a good correlation was shown between follow-up $^{18}F$-FDG PET/CT results and conventional evaluation in both corticosteroid-responding patients and in cases of persisting or relapsing disease (Figs. 9 and 10).

In a given clinical context, in a patient with histologically-proven SNS, $^{18}F$-FDG PET/CT may be used to monitor treatment response. PET/CT assessment of treatment response, which was evaluated principally for thoracic sarcoidosis [14,15,19,20], could be a new line of research in SNS further studies.

The differential diagnosis of SNS should consider other diseases such as tuberculosis, aspergillosis, actinomycosis, Churg-Strauss syndrome, mediastinal granulomatosis, ENT locations of Crohn disease and especially Wegener syndrome with generally more severe destructive lesions. Usually the clinical context and biopsy results lead to diagnosis of these other systemic granulomatosis diseases or even malignant tumors [1–10,12,15,18].

Further studies are necessary to improve the diagnostic and therapeutic procedures, to evaluate more completely the pronostic factors and to assess the natural history of this uncommon and probably underdiagnosed disease.

Despite these interesting preliminary results, several limitations of our study must be taken into account:

- its retrospective nature and the limited number of patients included;
- the possible bias related to the selection of patients with a severe phenotype of sarcoidosis;
• the absence of systematic and comparative assessment by CT, MRI, $^{67}$Ga scintigraphy and $^{18}$F-FDG PET/CT before and after treatment for all the patients.

Conclusion

SNS is an uncommon and probably underdiagnosed phenotype of sarcoidosis. Even if guided biopsy remains necessary for sarcoidosis confirmation, medical imaging plays an important role in diagnosis and therapeutic follow-up. CT features with nodules of the septum and/or turbinates are suggestive of SNS contrary to other nonspecific CT findings. CT imaging is directly related to severity, reversibility and course or progression of SNS and provide an original radiological staging system in order to predict patient clinical outcome. $^{18}$F-FDG PET/CT may be used for diagnosis assessment but also to monitor treatment response in a given clinical context, in a patient with histologically proven SNS. Prospective and long term studies are necessary to validate these preliminary results.

Conflicts of interest

The authors have no conflicts of interest.

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