Imaging features of extra-thoracic sarcoidosis: a pictorial essay

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Learning objectives

Extra-thoracic sarcoidosis shows widely different imaging features and can often mimic other pathological disorders. The aim of this poster is to describe radiological findings of sarcoidosis in central nervous system, abdomen and bones.
Background

Epidemiology

Sarcoidosis is a multi-systemic disorder of unknown cause, pathologically characterized by the accumulation of inflammatory cells forming non-caseating granulomas. Clinically, it could show a variable course [1]. 90% of patients show granulomas located in the lungs or in the related lymph nodes. However, lesions can affect any organ. Although there are different clinical phenotypes between racial groups, the disease affects all ethnicities, ages and sexes [2].

Normally, sarcoidosis occurs in both young men and women aged between 25 to 40 years while some studies show a major incidence in females. In about 30% of cases, the disease can also occur in patients over age 50, namely women have a second peak incidence own from 50 to 65 years of age. In this case, the disease shows different clinical features from those of younger patients [3-4].

The annual incidence varies widely according to the different country. In Northern Europe the estimated incidence is about 5-40/100,000, which is the highest value reported, while in Japan it is lower, with a value of about 1-2/100,000. Afro-Americans are 35.5/100,000 while white Americans are 10.9/100,000 [2]. Extratoracic disease behaviours are widely different between the different ethnicity, with a prevalence of cardiac and ocular diseases in Japanese, erythema nodosum in Northern European, ocular and granulomatous skin involvement in black patients [5-7].

Pathogenesis

For many studies, sarcoidosis is caused by exposure to environmental or infective agents in genetically susceptible individuals. Insecticides and musty odors have been characterized as risk factors involved in the development of the disease [8]. The role of genetic factors has been remarked by Rybicki et al. who confirmed a higher risk for first and second degree relatives of affected patients [9].

Multiple gene polymorphisms have been identified in sarcoidosis, with particular regard to HLA (Human leucocyte antigeone) polymorphisms. According to this hypothesis, sarcoidosis might be an antigen driven disease [10]. Sarcoidosis is characterized by the formation of non caseating granulomas, formed by a core of Th1 cell surrounded by fibroblasts, B-cells and CD8 lymphocytes. The granuloma formation starts with alveolar macrophages and dendritic cells activation by a putative antigen. Dendritic cells migrate to lymphnodes and cause Th1 amplification, whereas alveolar macrophages produce chemokines attracting B-cells and fibroblasts. Previously, sarcoidosis was considered a Th1 mediated disease, but new studies have also demonstrated the contribution of pro-
inflammatory cytokines (IL-23) and Th17 in the granuloma formation [11]. The factors determining granuloma resolution or progression are still unknown.
Findings and procedure details

Systemic sarcoidosis may affect any organ, with possible involvement of skin, eyes, bones, muscles, liver, spleen, brain, spine, kidneys and heart. In our Radiological Department, the most frequent cases of extra-thoracic sarcoidosis are located in the liver and spleen, in the brain and in the skeleton. Imaging appearance of sarcoidal nodules is often non-specific and it is important to study the possible differential diagnosis.

Neurosarcoidosis

Neurosarcoidosis affects about 27-37% of patients at autopsy, but it is diagnosed ante-mortem only in less than 10% of cases, because the clinical presentation depends on the site of the lesions [13].

The lesions are usually located in the base of the brain and sometimes also the optic and facial nerve are involved [13]. Sarcoidal nodules can be solitary or multiple with a ring-like appearance, showing enhancement after contrast injection in the activity phase. This appearance can simulate glioblastoma or metastases. Typically, in the periventricular and deep white matter, they are also visible as hyperintense lesions in T2-weighted images, simulating multiple sclerosis [14]. Leptomeningeal localizations are visible better after contrast injection, showing a diffuse enhancement. In spinal cord (Fig. 1 on page 8), especially in cervical and thoracic regions, lesions appear hypointense in T2-weighted MRI sequences with hyperintensity of the associated edema. They show enhancement on T1-weighted images after contrast injection [14].

Liver and spleen sarcodosis

Liver and spleen localizations are seen in 50-80% of autopsies, but often the patients are asymptomatic. Imaging demonstrates a hepato-splenomegalia, with homogeneous parenchyma [15]. In 5%-15% of cases, multiple nodular liver and spleen lesions (Fig. 2 on page 8, Fig. 3 on page 9, Fig. 4 on page 10, Fig. 5 on page 10), ranging from 1-2 mm to several centimeter in diameter, are visible and show a low signal on CT scan and on MRI, especially in T2-weighted fat-saturated images, even after contrast injection [16]. Splenic lesions (Fig. 6 on page 11) are more common and larger than the hepatic ones and they are found in about 69% of patients with hepatic nodules [15].

In about 30% of patients with systemic sarcoidosis, lymphadenopathy (Fig. 7 on page 12, Fig. 8 on page 12), smaller than 2cm, can also be observed in the porta hepatis, celiac axis and paraaortic region [15, 17]. The hepatic and splenic nodules and the abdominal lymph nodes demonstrate an increased FDG uptake on PET and they should be differentiated from other diseases, such as metastases, lymphoma and
granulomatous or mycobacterial infections [18]. In these cases, clinical and laboratory data are useful.

**Renal sarcoidosis**

Renal sarcoidosis affects about 7-22% of patients at autopsy. It usually displays striated nephrograms on contrast-enhanced CT, in cases of interstitial nephritis [15]. Rarely, CT and MRI show hypo-attenuating multiple nodules, ranging from 2 cm to 3 cm, that simulate lymphoma or metastasis. Kidneys may appear both bigger than normal and atrophic [13].

**Muscle-skeletal sarcoidosis**

The skeleton is affected in about 1-13% of patients with generalized disease, complaining of bone and joint pain. Sarcoidosis usually involves the phalanges of the hands and feet; conventional radiography, performed in symptomatic patients, demonstrate either "lacy" osteolytic or osteosclerotic multiple lesions, where the latter is less frequent [19]. Large bones and axial skeleton involvement is uncommon. In large bones, lesions usually demonstrate a lytic appearance with indistinct or well-defined margins at conventional radiography. In the vertebrae (Fig. 9 on page 13), both osteolytic lesions with sclerotic borders and diffuse osteosclerotic localizations are possible [13, 19-20]. Lesions can be located in one or more contiguous or non-contiguous vertebrae and they can also affect the pedicles. Patients may complain of arthralgias in knees, ankles, elbows and wrists, but joint radiograms are usually negative or demonstrate non-specific signs of osteoporosis and soft-tissue swelling [19].

These lesions usually demonstrate an uptake on bone scintigraphy, even before the lesions are visible at conventional radiograms [13]. The use of CT and MRI is rare and it is usually performed to help differential diagnosis from other pathologies with skeletal involvement, such as osseous metastases, lymphoma, myeloma and tuberculosis [19].

Sarcoidosis may also affect the muscles with myopathic or nodular type involvement [13]. On MR, sarcoid nodules show hypo-intense fibrotic central areas, with marginal peripheral areas hyper-intense on T2-weighted images with enhancement after gadolinium. These appearances may mimic a soft-tissue tumor. In the myopathic type, the involved muscles demonstrate a high signal intensity on T2-weighted images [19].

**Skin involvement**

Skin lesions occur in about 25% of patients. The clinical manifestation (Fig. 10 on page 14) are variable and the two most important types are: in the acute phase, erythema nodosum with soft red swelling on the legs, and in chronic phase of disease, lupus pernio with "indurated plaques" on the face [13].
Eyes

Finally, one of the most common extra-thoracic localization is represented by eyes (Fig. 11 on page 15). About 80% of patients affected by sarcoidosis have ocular involvement with bilateral uveitis [1]. Generally, these patients are not studied with radiological exams.
Fig. 1: MR images show spinal cord involvement in a 54-year-old male. T2-weighted image (a) demonstrates an extensive area of edema in the spinal cord (white arrow); unenhanced T1-weighted image (b) only shows swelling of the spinal cord. On enhanced T1-weighted acquisitions, a peripheral enhancement (curved white arrow) can be depicted (c), suggesting meningeal involvement.

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Fig. 2: A 61-year-old female patient affected by pulmonary biopsy proved sarcoidosis. Routine abdominal ultrasound exam (a and b) shows multiple, small, randomly distributed, hypoechoic nodules in the liver parenchyma.

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Fig. 3: Liver MRI of the same patient of figure 2, which demonstrates multiple, scattered, small, hyperintense nodules on T2-weighted images (a and d) and on diffusion-weighted images (b and e). After gadolinium administration above-mentioned lesions appear hypointense (c and f).

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Fig. 4: A 66-year-old female patient affected by breast cancer and sarcoidosis. Chest CT-scan shows pulmonary sarcoideal localizations and hilar lymphadenopathy (a and b). Abdomen CT scan demonstrates a slightly hypo-attenuating small liver lesion (c; white arrow) with associated enlarged lymph-nodes (d). MRI (e and f) also shows both liver lesion (e; white curved arrow), which appears hypo-intense in hepatobiliary phase, and lymph-nodes (f).

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**Fig. 5:** Same patient of figure 4. Abdomen CT scan of suspected hepatic lesion pre- (a) and post-steroid therapy (b). The previously reported hypodense liver lesion (a; white arrow) is not appreciated anymore during follow-up after six months.

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**Fig. 6:** Contrast-enhanced CT images of a 32-year-old female (a and b) demonstrate multiple, small, hypoattenuating nodular lesions randomly distributed in splenic parenchyma. In c and d, MR exam of a 61-year-old female depicts splenic sarcoidal involvement. Multiple hypointense target lesions are shown on T2-weighted image (c) and on enhanced T1-weighted image (d), creating an heterogeneous parenchymal appearance.

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**Fig. 7:** CT scan of a 55-year-old female demonstrates multiple enlarged lymph-nodes located in mediastinum, especially in right and left hilum (a), and in abdomen - in celiac axis (b), in para-aortic and paracaval region (c) and in the mesentery (d).

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Fig. 8: Incidental sarcoidosis diagnosis in a 59 year-old female complaining acute abdominal pain. Unenhanced CT scan shows a gallbladder's calculus (a; white arrow) and some peri-pancreatic lymph nodes (b; white arrowhead); than, CT scan extended through the chest (c) showed multiple, small subpleurical nodules. Histological exam confirmed diagnosis of sarcoidosis for the mentioned peri-pancreatic lymph nodes.

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Fig. 9: Axial skeleton involvement of a 49 year-old female. Axial CT images (a, b and c) show multiple diffuse osteosclerotic lesions in cervical, lumbar and sacral vertebrae; sagittal (d) and coronal (e) reconstructions demonstrate lesions in contiguous and non-contiguous vertebrae.

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Fig. 10: Skin involvement in three different patients. Sarcoidal nodules in face (a), arm (b), abdominal wall (c) and legs (d).

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Fig. 11: 62-year-old female with sarcoidosis. Digital retinal scan shows "Punched-out" choroidoretinal lesions (a and b).

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Conclusion

Imaging findings of the extra-thoracic sarcoidosis are extremely variable and can often simulate other malignant diseases. Sarcoidosis should be considered in the differential diagnosis of multiple lesions of brain, abdomen and bones, in patients with suspected or proved disease. Radiologists, by correlating imaging and clinico-pathologic findings, have an important role in diagnosis and follow-up of sarcoidosis, in order to reduce morbidity and mortality.
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