Imaging methods for pulmonary sarcoidosis

Abstract

Sarcoidosis is a chronic systemic granulomatous disease of unknown etiology. In more than 90% of patients with diagnosed sarcoidosis, mediastinal and hilar lymph nodes are affected. The objective of this paper is to discuss the most important chest imaging methods in pulmonary sarcoidosis. A chest X-ray remains the method of choice at both the diagnostic stage and during follow-up of the disease progress. High-resolution computed tomography allows for a more thorough description of lesions in terms of their location. Research demonstrates the superiority of FDG PET over both aforementioned techniques in the assessment of active inflammatory lesions. Magnetic resonance imaging is currently being used in diagnosing cardiac sarcoidosis. Although EBUS constitutes the basic diagnostic tool, the invasiveness of the method results in it not being used when monitoring the activity of the disease.

Key words: X-ray, HRCT, PET/CT, MRI, scintigraphy, pulmonologist point of view

Introduction

Sarcoidosis is a chronic granulomatous disease of unknown etiology [1]. In more than 90% of patients with diagnosed sarcoidosis, mediastinal and hilar lymph nodes are affected [2, 3]. The diagnosis is based on the evaluation of clinical, radiological, and histopathological features [7]. The objective of this paper is to discuss the most important chest imaging methods in pulmonary sarcoidosis and to determine their role in the process of diagnosing the disease and monitoring its activity.

Conventional X-ray

The method of choice which should be applied in each and every patient with a clinical suspicion of sarcoidosis is a conventional X-ray [8]. Its unquestionable advantages include its wide availability and low cost. Despite the development of other techniques, X-ray imaging remains the first examination recommended in the diagnostic procedure, and a gold standard in monitoring the activity of the already diagnosed disease [8]. It is recommended to apply relevant scales in order to systematise and standardise X-ray images. One of the best-known scales is the one proposed by Scadding/Siltzbach in 1961 in which patients were classified according to one of four groups based on lesions visible in the chest X-ray (i.e. enlarged hilar lymph nodes, the presence of parenchymal infiltrations, and features of fibrosis) [9]. The first group included patients with isolated hilar lymphadenopathy; the second — subjects with accompanying parenchymal infiltrations; the third — subjects without lymphadenopathy, but with lesions in the lung parenchyma; the fourth — patients with fibrotic lesions. On the basis of the group of patients (n = 136), Scadding rated the incidence of individual groups in the population of patients with sarcoidosis and the probability of spontaneous remission in each of them [9]. This scale was accepted and has been widely used to date. Another classification method, which was applied in the analysis of pneumoconiosis and adapted by Muers et al., consists of the division of both lung...
lobes into zones and in the evaluation of the profusion of individual types of lesions in the zones, specifically reticulonodular changes, masses, confluent, and fibrosis [10, 11]. The chest X-ray and the pulmonary function test (PFT) constitute the main tools for monitoring the activity of sarcoidosis. Boros et al. retrospectively analyzed the results of functional tests in 830 patients with diagnosed sarcoidosis. They analyzed them based on the stage that they were in determined by the Scadding/Siltzbach classification of chest X-ray [12]. Despite the parenchymal changes visible in the chest X-ray in about three-quarters of patients (stages II–IV), only 7% had a restriction in lung volume. At each stage (according to Scadding/Siltzbach), the lung transfer factor for carbon monoxide was impaired and static lung compliance was reduced [12]. Despite an established position which identifies X-ray imaging as a tool for monitoring the disease, the discussion devoted to decision making with reference to the onset of therapy based exclusively on the basis of radiological changes without accompanying lung function disorders is still ongoing. Pietinalho et al., in their study of patients with recently diagnosed sarcoidosis that had no deviations in the functional tests, applied a 3 months’ therapy with prednisone, which was followed by inhaled budesonide for 15 months. They demonstrated that patients, who at the onset of the therapy had stage II/III sarcoidosis and received treatment, experienced specific benefits in terms of FVC and DLCO 5 years after the study. Furthermore, they required glucocorticosteroid therapy much later than when compared to the placebo group [5]. Considering the possible side effects of the therapy, it is recommended to exercise caution when deciding about the beginning and/or continuation of treatment based exclusively on the advancement of the disease as evaluated in the chest X-ray. Figure 1 presents typical conventional chest X-ray picture of stage II sarcoidosis.

**High resolution computed tomography**

A method that has become much more accessible is computed tomography. High-resolution computed tomography (HRCT), which is a method of choice in the evaluation of interstitial diseases, demonstrates a considerable superiority over the CT with contrast in the detection and evaluation of even subtle lesions in lung parenchyma [14]. Routine diagnostic protocols make use of thin-layer scans, from 1 to 1.5–2 mm [15]. In the past, the “so-called” sequential HRCT scans were used where layers were visualized every 10 mm from the apex of the lung to its base at full inspiration. As a result, as much as 90% of the lung was not seen on imaging. Thanks to advanced technical devices (multiple detector computed tomography), the rotation time necessary to generate the image has been shortened to 0.28–0.5 seconds (depending on the type of the apparatus). The use of spiral acquisition enhanced the scan sensitivity and minimised respiratory and pulsatory artefacts [15, 16, 17]. According to the 1999 ATS/ERS/WASOG guidelines which are still valid, there are three indications to perform a CT scan: a) if there are no lesions in the X-ray, but there is a clinical suspicion of sarcoidosis (stage 0); b) if there are atypical clinical or radiological symptoms; and c) in order to diagnose possible complications [1]. There are two typical findings in sarcoidosis in HRCT. Firstly, there is hilar and mediastinal lymphadenopathy which is most frequently bilateral and symmetrical. Secondly, there are nodules (both micronodules [2–4 mm in diameter] and macronodules) which can be located along bronchovascular bundles, interlobular septi, interlobar fissures, and in the subpleural region (Figure 2) [18]. In advanced stages, the features of fibrosis are visible and can include honeycombing, architectural distortion, traction bronchiectasis, and/or volume loss. Most frequently, lesions in sarcoidosis demonstrate predilection to the upper and middle fields [18].
The increasingly widespread application of the HRCT scan is associated with better-known radiological characteristics of sarcoidosis. Cases of histopathologically confirmed sarcoidosis with atypical manifestations in the HRCT scan are becoming more and more frequent. Sarcoidosis has been dubbed “the great imitator”, just like tuberculosis before it [19, 20]. More and more authors present cases of patients with new CT patterns [21]. Radiological manifestations less frequently encountered in sarcoidosis but seen on HRCT include unilateral or isolated lymphadenopathy, parenchymal infiltrations in the form of conglomerate masses, single nodules larger than 1 cm, confluent alveolar opacities (alveolar sarcoid pattern), and cavernous changes [18]. An interesting symptom is that of granulomatous nodules coalescing together to form larger ones, which was described for the first time by Nakatsu et al. [21]. Bigger nodules are surrounded by smaller satellite nodules forming a structure resembling stars forming a galaxy, hence the galaxy symptom mentioned by the authors. In the study, this symptom was found in 16 out of 59 subjects. The 3-mm collimation was used for the evaluation of the larger nodules (instead of conventionally used 1–2 mm layer) which, in the authors’ opinion, had a positive effect on the visualisation of peripheral micronodules, bronchioles, and branches thereof [21]. Another relatively new image of sarcoidosis in HRCT is the “sarcoid cluster sign” which was first described by Herráez Ortega. This sign is characterised by the accumulation of small punctiform nodules on the periphery of the lungs [22]. However, both “galaxy” and “cluster” signs can be seen in pulmonary TB and silicosis as well (Figure 3) [23–25].

According to the authors, the majority of such lesions are arranged in circular groups and are not located directly in subpleural peripheral regions of the upper and middle fields of the lungs [22]. Other patterns visible in HRCT have been also described such as “reversed halo” ring-shaped areas of consolidation with a central ground-glass attenuation [26–29]. Besides the precise assessment of the profusion of interstitial lesions, HRCT also indirectly allows to assess the prognosis for patients suffering from sarcoidosis by differentiating between reversible and irreversible lesions [30]. Lesions such as micronodules, nodules, or peribronchovascular thickening can withdraw spontaneously or under treatment. On the other hand, consolidations, ground-glass opacification, or linear opacities are characterised by variable reversibility. Irreversible lesions include architectural distortion, bronchiectasis, honeycombing, and emphysematous bullae (Figure 4) [31]. The role of HRCT in diagnosing sarcoidosis, particularly in cases which are difficult to diagnose, is currently broadly recognised. There is an ongoing discussion regarding the role of computed tomography in the monitoring of the activity of...
the disease. This discussion is attempting to determine whether it should be repeated routinely in every patient, whether it should be applied only in the case of more advanced lesions visible on an X-ray, and whether it should be used in the presence of functional disorders. Ziora et al. analysed a group of patients who would have fallen into group 1 according to the Scadding scale. After examining these patients by HRCT, they assigned them to two separate subgroups: patients with lesions in pulmonary parenchyma, and patients without parenchymal lesions [32]. Both groups underwent regular functional testing and X-ray scans. During a 2-year long observation, no statistically significant difference was observed between the functional test results. Moreover, the share of patients with radiological stabilisation, progression, or improvement was not different in both groups [32]. Numerous studies have demonstrated the superiority of HRCT in detecting lesions corresponding to fibrosis and in diagnosing more advanced stages of the disease. Chest X-ray scans revealed fibrosis in 5–10%, whereas CT scans resulted in such changes being described in as many as 20–50% of patients [33–35]. Currently, there are no clear data which would allow to determine whether repeated HRCT scans in patients suffering from sarcoidosis have any effect on making therapeutic decisions. Levy et al. recommend repeated HRCT scans if the clinical image changes or complications are suspected [36–37]. Unlike X-ray scans, some lesions visible in HRCT demonstrate a relationship with pulmonary function disorders [38–40]. Drent et al. demonstrated correlations between features visible in HRCT such as thickening of the bronchovascular bundle, intraparenchymal nodules, septal and non-septal lines, or focal pleural thickening on one hand, and results of respiratory functional tests on the other [38]. However, such a relationship has not been demonstrated for consolidations, ground-glass opacifications, or enlargement of lymph nodes. Furthermore, the study also demonstrated the superiority of the HRCT scan over a conventional X-ray scan in terms of their relationship to the respiratory function parameters of the lungs [38].

**Gallium-67 scintigraphy**

Another imaging method used in sarcoidosis is Gallium-67 scintigraphy (Ga-67), albeit less and less frequently so. Its sensitivity in detecting pulmonary sarcoidosis ranges from 60 to 90% [41, 42]. For patients suffering from sarcoidosis, two gallium uptake patterns are characteristically used known as lambda and panda, and are named as such because of their shapes [43]. The lambda pattern comprises the gallium uptake in the parahilar and infrahilar lymph nodes along with the paratracheal lymph nodes on the right-hand side [43]. The panda pattern is associated with a symmetrical uptake in parotid and sublingual salivary glands. The constellation of the lambda and panda pattern uptake is recognised as very characteristic for sarcoidosis [17, 44]. Gallium-67 scintigraphy is more sensitive than an X-ray scan and can be applied for the evaluation of the staging of the disease activity, for the assessment of treatment results, and for the prediction of relapses. However, a more widespread application of this method is limited due to its restricted availability, cost, exposure to radiation, and duration [43].

**Scintigraphy with other tracers**

It is also possible to use scintigraphy with other tracers. Somatostatin receptor (SR) scintigraphy is based on the uptake of octreotide derivatives, such as 99mTc-octreotide or other somatostatin derivatives, by somatostatin subtype 2 receptors. The application of this method affected therapeutic decisions of Piotrowski et al., who in their study compared the predictive value of scintigraphy with 99mTc-octreotide and biomarkers (SACE, CRP, markers of calcium metabolism, lymphocytes in BALF, 8-isoprostane in exhaled...
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Single-photon emission computed tomography

The image of classical scintigraphy is obtained by projecting a three-dimensional object onto a plane. This technique is extended by the use of several gamma cameras rotating around the patient, which allows to obtain an image of selected layers. This method, referred to as single-photon emission computed tomography (SPECT), was applied by Vis et al. [47]. The SPECT/CT scan was performed in a group of 10 patients after the administration of technetium-99m(99mTc)-labelled infliximab. The patients demonstrated a correlation between the radiomarker accumulation in SPECT and the lab parameters (sIL-2R, ACE level in serum, ACE Z-score, CD4/CD8 level in BAL), functional test disorders, as well as the PET scan with fluorodeoxyglucose. The study demonstrated variable selective accumulation of the radiomarker in SPECT, which correlated positively with the lab markers and negatively with the pulmonary function, as well as with the PET scan [47]. A similar result was also obtained by — without limitations — Galli et al., who demonstrated a negative correlation between the uptake of 99mTc-labelled infliximab and the activity measured in the PET scan. The scan with the application of 99mTc-labelled infliximab with the TNF alpha inhibitor may be used in the future to select groups of patients where this therapy will be effective. However, further research into this subject is required [48].

Positron-emission tomography

Another study in the field of nuclear medicine is positron-emission tomography (PET). Simultaneous use of computed tomography allows to shorten the duration of the scan and additionally improve the accuracy of descriptions of anatomical changes detected (PET/CT) [49]. The most commonly used marker is 18F-FDG, which is a glucose analogue. Transported through the cell membrane inside the cell, it is subjected to phosphorylation by hexokinase. Consequently, a molecule of 18F-FDG-6 phosphate is formed and it is not metabolised any further. The accumulation of macrophages exhibiting increased metabolism in the area of sarcoid granulomas causes an uptake of the administered marker by glucose transporters GLUT-1 and GLUT 3 [50]. The superiority of 18F-FDG PET/CT over Gallium-67 scintigraphy was demonstrated by Braun et al. in their study. They confirmed the very high sensitivity of the former in detecting active foci within the chest reaching 100%, as compared to 71% when scintigraphy is applied [49]. In addition, the advantages of FDG-PET include having 3 times lower radiation dose and shorter time of procedure [51].

The research points to a good correlation between an X-ray and PET scan in the case of higher stages of sarcoidosis according to the Scadding scale [52]. A chest X-ray showing no lesion, which stands for stage 0 in this classification, does not exclude a positive result of the PET scan. In the study of Mostard et al., in 27% of patients with no symptoms in the chest X-ray, a marker uptake was detected. In advanced stage 4 patients, activity was also visible in the PET scan for the majority of subjects (88%) [51]. The study also compared HRCT (on the basis of the score proposed by Oberstein) with images obtained in PET scans (occurrence/non-occurrence of changes). In this case, patients with the score 0, according to Oberstein, did not have any changes visible in the PET scan. Conversely, in subjects where HRCT scan revealed features of fibrosis, the activity was frequently visible in the PET scan. This may be indicative of a still active and potentially reversible inflammatory process [52]. The selection of patients in which the inflammatory process is still ongoing despite fibrosis having been found may allow clinicians to choose the optimum treatment in this group of patients. PET can be applied in the diagnostic procedure of the disease; it allows to detect active inflammatory lesions in patients with symptoms,
even if other diagnostic methods give negative results. PET also identifies the best locations for biopsy. It is used for monitoring the activity of the disease, and diffuse parenchymal infiltrations detected in this scan allow to predict further loss of the pulmonary activity [53, 54]. Sobic-Saranovic et al. demonstrated that in a group of 90 patients subjected to 18F-FDG PET/CT scans, 81% of them had decisions regarding further treatment made based on the scan result. In the majority of patients in which an increased marker uptake was observed in the PET scan, the previously administered dosage of glucocorticosteroids was increased or a new medication was used. On the other hand, patients with a negative scan result had their dosage reduced or the medications were discontinued altogether [55]. PET can be helpful in deciding whether patients with severe sarcoidosis should receive biological treatment. In the study by Vorselaars et al., a PET scan was performed prior to the onset of therapy and then again after 26 weeks [56]. The second follow-up scan revealed a reduction of the standardised uptake value in the region of mediastinum by 2.97 (P < 0.0001), and in the region of lung parenchyma by 3.93 (p < 0.0001) as compared to the output SUV values. The higher the SUV values were prior to the administration of infliximab, the greater the improvement was in terms of the FVC values observed after treatment [56].

The role that PET can play in the evaluation of the activity of the disease in the future is pointed to by the study comparing the serological markers of the activity of the disease used so far, such as ACE and soluble interleukin 2 receptor [57]. In a retrospective study, 36 patients with recently diagnosed symptomatic disease had a PET scan performed and their levels of ACE and sIL-2R were measured. F-FDG PET was positive in as many as 34 out of 36 patients (94%), elevated levels of ACE were observed in 13 patients (36%), and increased sIL-2R in 17 (47%) [57].

Additional benefits offered by a PET scan also include the extent of the examination which covers the entire body and can sometimes allow to find sarcoid foci in other organs. This scan can constitute an alternative for patients with suspected cardiac sarcoidosis in whom an MRI scan cannot be performed (e.g. due to the presence of a pacemaker or ICD) [53].

Unfortunately, the uptake of 18F-FDG occurs in sarcoid as well as neoplastic lesions. Therefore, this examination is not suitable for differentiating between sarcoidosis and neoplasms. A group of Japanese researchers raised the subject of using another marker, 18F-FMT (Fluorine-18-α-Methyltyrosine) [58]. The study covered a group of 24 patients with sarcoidosis that also had an additional suspicion of a neoplastic process occurring. The control group included patients with diagnosed lung cancer. In all the subjects from the examined group, the uptake of 18F-FDG in lymph nodes was observed, whereas 18F-FMT was not accumulated in them. In extranodal organs, such as the liver, spleen, and bones, the PET scan result was positive if the former marker was used and negative with the latter. The neoplastic disease was not diagnosed in any of the study subjects [58]. The mean standardised uptake values (SUV) in the examined group for 18F-FDG and 18F-FMT were 5.01 ± 2.15 and 0.77 ± 0.24 respectively, whereas in the control group consisting of patients suffering from the neoplastic disease the values were 6.34 ± 2.52 for 18F-FDG and 1.54 ± 0.82 for 18F-FMT. On the basis of these results, the authors concluded that the additional use of 18F-FMT besides 18F-FDG may facilitate the differentiation between sarcoid and malignant changes [58].

Like is the case with Gallium-67 scintigraphy, the common use of PET and PET/CT scans is limited due to their limited availability and high costs. Figures 5 and 6 present PET results of patients with sarcoidosis.
Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a recognised imaging method in the diagnostic procedure of cardiac sarcoidosis and in evaluating changes in the structure of bones or in the central nervous system, but it is rarely applied for the evaluation of the lung parenchyma due to the limitations of this method associated with the presence of air in the lung tissue and the physiological motion of the chest (cardiac pulsation, respiration) [17, 59–61]. Most studies have demonstrated the superiority of HRCT over MRI in the evaluation of interstitial lesions [17]. Brady et al., who used the technique of late enhancement in magnetic resonance imaging in their work, obtained comparable results when using HRCT and MRI in the description of lesions suggestive of fibrosis [62]. Consistency between MRI and HRCT in the diagnosis of pulmonary sarcoidosis was also confirmed by Chung et al., who evaluated images in terms of the presence of interstitial changes, reticulations, nodules, and condensations according to a 3-point scale in the division into lobes. Furthermore, they noticed that a better correlation between the scans related to the upper lobes [63]. In relation to lymphadenopathy, MRI is a technique demonstrating a similar value to computed tomography in detecting enlargement of hilar and mediastinal lymph nodes. Nevertheless, MRI facilitates the evaluation of the extent of lymphadenopathy as it is differentiated better from the vascular system of the lungs [64]. Chung et al., referred to above, analysed MRI scans performed in the heart examination protocol and noticed that some patients with sarcoidosis had lymph nodes with a specific appearance: a hypo-intensive signal inside and a hyper-intensive rim. This symptom was called a dark lymph node sign by the authors. Retrospectively, it occurred in 49% of patients from the examined group [65]. New signs being described in MRI scans give hope for better characteristics of sarcoidosis based on MRI and potentially, for a more common use of this method in the future.

Endoscopic ultrasonography

Many studies assessing the possibility of using endoscopic ultrasonography in the evaluation of lymph nodes in patients suffering from sarcoidosis have been conducted in recent years. EBUS/EUS already enjoys an established position in the diagnosis of sarcoidosis [4–6]. EBUS allows to evaluate 2R, 4R lymph nodes on the right-hand side, 2L, 4L lymph nodes on the left-hand side, as well as paratracheal and subcarinal regions (group 7). Additionally, EBUS helps to access hilar lymph nodes (group 10) and the interlobar region of group 11. An EUS scan allows to examine the subcarinal region 7, the paraesophageal region 8, and region 9. It is also possible to access the paratracheal region on the left-hand side (4L), and to partially assess the left hilar region as well (10 L). A meta-analysis covering 14 studies (which covered 2097 subjects in total) demonstrated a high diagnostic efficiency of this method.
reaching 79%. Its sensitivity and specificity were estimated to be 84% and 100%, respectively [66]. The percentage of positive results obtained thanks to the EBUS-TBNA method is higher in patients with stage 1 than 2, which probably results from a higher density of granulomas in stage 1. EBUS allows not only to collect the material, but also to evaluate lymph nodes. In their study, Erol et al. compared the image of lymphadenopathy in tuberculosis and sarcoidosis [67]. Lymph nodes in sarcoidosis formed conglomerates more often than in tuberculosis and were also characterised by higher homoechogenicity. In tuberculosis, lymph nodes were more frequently oval in shape and more heterogenous, and their foci of necrosis were bigger as well. Due to the fact that both diseases belong to the group of granulomatous diseases, lymph nodes had a similar vascular pattern [67]. Agrawal et al. compared inter alia metastatic lymph nodes with lymph nodes enlarged due to sarcoidosis. In this case, features that differentiated lymph nodes in the course of proliferative diseases from sarcoid ones were predominantly heterogenicity, clear margins, signs of coagulative necrosis, and the presence of the central hilar structure (CHS) [68]. Regrettably, due to the invasiveness of this method, it cannot be practically used in the monitoring of the activity of the disease [69].

Transthoracic ultrasound scan

Nowadays, advanced high-resolution ultrasound apparatuses with facultative employment of colour Doppler allow to examine the mediastinum and the heart region. In their study, Hirche et al. compared the application of a transthoracic ultrasound scan with a conventional X-ray scan [70]. The use of an ultrasound scan in the evaluation of mediastinal lymph nodes proved to be up to 90% effective. Lymph nodes in patients who on the basis of a chest X-ray had been assigned to groups 1–3 according to the Scadding score were particularly well visible. This is in contrast to group 4, in which the ultrasound visualisation of lymph nodes turned out to be insufficient. A benefit stemming from this method is the fact it allows for a morphological assessment of the lymph nodes, which is not possible based on an X-ray scan. In the study summary, however, the authors emphasise that the sensitivity of this method in detecting lymphadenopathy is highly dependent on the experience and skills of the operator and the class of the device [70].

Conclusion

Currently, we have observed constant progress in the field of imaging. Thanks to the development of advanced techniques, it is possible to understand sarcoidosis better, to grasp its natural course and the effect of treatment onto the activity of the changes. A chest X-ray scan remains the basic examination at the stage of diagnosis, as well as in the subsequent monitoring of the disease. High-resolution computed tomography allows for a more precise description of lesions with reference to their location. Studies point to the superiority of FDG PET over both methods in the evaluation of active inflammatory changes. The use of other markers in PET, such as FAMPT for example, may be helpful in differentiating between sarcoid and malignant changes in the future. Ultimately, deciding which diagnostic method is best for each individual patient is the responsibility of the clinician. The decision should be made on the basis of an analysis of possible profits and losses considering the repeatability of the results, availability of the method, its invasiveness, radiation exposure, cost, and possible influence on therapeutic decisions. It is worth emphasizing, that the average radiation dose in the case of X-ray imaging (PA and lateral view) ranged from 0.05–0.25 mSv, in the case of HRCT from 2.1–3.5 mSv, and in the case of PET from 7–11.5 mSv. Bearing in mind that most of the patients with sarcoidosis are between the ages 20 and 40 years old and will never require treatment, the decision about repeated studies involving a high dose of radiation should be made prudently [72].

Conflict of interest

None declared.

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