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K Guziejko and others

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Multiorgan sarcoidosis as a diabetes insipidus mask

Katarzyna Guziejko[1], **Łukasz Minarowski**[1], **Agata Piłaszewicz-Puza**[2], **Anna Szumera-Ciećkiewicz**[3] and **Robert Marek Mróz**[1]

[1]2nd Department of Lung Diseases and Tuberculosis, [2]Department of Medical Pathomorphology, Medical University of Bialystok, Bialystok, Poland, and [3]Department of Pathology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Correspondence should be addressed to K Guziejko
Email
kguziejko@wp.pl

Summary

Sarcoidosis is an inflammatory, multisystem disease with an undetermined etiology. The presence of noncaseating granulomas in involved organs is a characteristic pathomorphological feature. Sarcoidosis, like a chameleon, can mimic different medical conditions. Although the lungs are most commonly involved, extrapulmonary manifestations can influence any system. The clinical course of the disease may differ. Immediate initiation of glucocorticosteroid therapy is important when critical organs are impaired. A case of a patient with sarcoidosis whose first clinical symptoms were related to diabetes insipidus (DI) was presented. The diagnosis of multiple organ sarcoidosis was delayed because of an adequate response to treatment with vasopressin. The multidisciplinary diagnostic approach validated the involvement of the pituitary gland, lungs, lymph nodes, bones, and subcutaneous tissue. The presented case emphasizes the critical importance of the multifaceted differential diagnosis of patients with DI.

Learning points

- Sarcoidosis usually affects the lung but can also be a multisystemic disease.
- The assessment of the extension of sarcoidosis remains complex.
- A multidisciplinary approach must identify all-organ involvement and initiate appropriate sarcoidosis treatment.
- Diabetes insipidus (DI) can be the first symptom of a systemic granulomatous disorder.
- In the differential diagnosis of DI, a comprehensive assessment of rare causes of endocrine disorders, including extrapulmonary sarcoidosis, should be considered.

Background

Sarcoidosis (also known as Besnier–Boeck–Schaumann disease, BBS disease) is an inflammatory disease characterized by noncaseating granulomas in the affected organs (1, 2, 3). The estimated incidence of BBS disease ranges between 1 and 40 cases per 100 000 individuals (4). Many studies have assessed the immunopathogenesis of sarcoidosis, but the exact stimulus that induces the disease remains elusive. Environmental, infectious, and genetic factors may trigger pathological inflammation and disease development (3, 5, 6). The formation of sarcoid granulomas involves macrophages, epithelioid cells, multinucleated giant cells, and T and B lymphocytes (1, 2, 3, 7). BBS disease is usually diagnosed in young and middle-aged adults (1, 3, 4, 8). An initial assessment of all patients with suspected sarcoidosis should include a careful examination of all potentially affected organs and systems (6). The lungs are involved in approximately 90% of patients (2, 4, 6). The extrapulmonary manifestations of sarcoidosis are estimated in 30% of cases (2). Other commonly impaired organs are the lymph nodes, skin, eyes, liver, spleen, and heart (1, 6, 8). Neurosarcoidosis (NS) occurs in 3–20% of patients with systemic sarcoidosis

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(4, 5, 8, 9) and may involve the cranial nerves, meninges, brain parenchyma (especially the hypothalamic region), spinal cord, peripheral nerves, and muscles (3, 4, 10). The endocrine signs of sarcoidosis include diabetes insipidus (DI), hypothalamic hypopituitarism, amenorrhea–galactorrhea, hypogonadotropic hypogonadism, secondary hypothyroidism, and diffuse goiter or a solitary thyroid nodule (5, 8, 10).

The disease may resolve spontaneously in most patients with sarcoidosis (1). However, therapy is necessary for life-threatening and serious symptoms of multiorgan disease (2).

We reported a history of a 38-year-old male patient with multiorgan sarcoidosis, whose first clinical symptoms resulted from the impairment of the pituitary gland function. The assessment of hypothalamic–pituitary axis function verified central DI. Systemic evaluation and a multidisciplinary diagnostic approach also showed the involvement of the lungs, lymph nodes, bones, and subcutaneous tissue in sarcoidosis. Initially, the patient was treated using desmopressin, but after the diagnosis of multiorgan sarcoidosis with impaired pituitary function, glucocorticoid therapy was immediately started. The presented case emphasizes the importance of a multifaceted differential diagnosis of DI in determining the best therapeutic option for the patient.

Case presentation

A 38-year-old male patient was admitted to the Department of Lung Diseases and Tuberculosis with suspicion of sarcoidosis. A year earlier, the patient was hospitalized at the Internal Medicine Department of the District Hospital owing to polyuria (7000 mL), polydipsia, and fatigue. Symptoms worsened in the 4 weeks before admission to the hospital. DI diagnosis was made, and treatment with desmopressin (60 mg twice a day) was initiated. The patient was recommended for follow-up visits to the endocrinology and lung diseases outpatient clinic but did not follow the recommendations because symptoms on the desmopressin treatment reduced. After 12 months of desmopressin treatment at the Department of Internal Medicine and Metabolic Diseases of the University Hospital, a reassessment of the hypothalamic–pituitary function verified central DI (Tables 1 and 2). Desmopressin therapy was increased to 120 mg twice daily. The resolution of polydipsia and polyuria was attained. The patient's history also reported pharmacologically controlled hypertension with amlodipine 5 mg daily and ramipril 5 mg daily. Exposure to possible occupational or environmental factors was excluded.

Table 1 Laboratory tests.

Parameters	Result	Normal range
ACTH (pg/mL)	33.83	7.20–63.30
Cortisol (μg/dL)	13.3	
FSH (mIU/mL)	4.03	0.95–11.95
LH (mIU/mL)	4.87	0.57–12.7
TSH (μIU/mL)	0.590	0.350–4.940
fT3 (pg/mL)	3.48	1.71–3.71
fT4 (ng/dL)	0.92	0.70–1.48
IGF-1 (ng/mL)	214.00	
AFP (ng/mL)	3.04	0.89–8.78
Testosterone (nmol/L)	28.95	1.63–34.00
HCG-β (mIU/mL)	<2.3	0.0–5.0
Ca^{2+} (mmol/L)	2.56	2.10–2.70
Ca^{2+} in the 24-h urine collection		3.0–6.0
Concentration (mmol/L)	1.59	
Excretion (mmol/24 h)	5.57	
ACE (U/L)	5.6	12.0–68.0
Arterial blood gases		
pH	7.485	7.35–7.45
pCO_2 (mmHg)	28.5	35.0–45.0
pO_2 (mmHg)	87.6	65.0–100.0
$HCO3^-$ (mmol/L)	23.6	21.0–26.0
O_2Sat (%)	97.4	94.0–98.0
WBC (×10³/μL)	4.72	4.00–10.00
NEU (×10³/μL)	3.47	1.90–7.50
LYM (×10³/μL)	0.57	0.90–4.50
MONO (×10³/μL)	0.52	0.10–1.00
EOS (×10³/μL)	0.11	0.05–0.50
BASO (×10³/μL)	0.03	0.00–0.20
RBC (×10⁶/μL)	4.61	4.50–6.00
HGB (g/dL)	14.7	14.0–18.0
HCT (%)	41.8	40.0–54.0
MCV (fL)	90.7	80.0–94.0
MCH (pg)	31.9	27.0–34.0
MCHC (g/dL)	35.2	31.0–37.0
PLT (×10³/μL)	306	130–350
Na^+ (mmol/L)	137	136–145
K^+ (mmol/L)	4.6	3.5–5.1
Plasma osmolality (mOsm/kg)	277	275–295
Urine osmolality (mOsm/kg)	553	50–1200
Urine test		
Color	Yellow	
Turbidity	Clear	
pH	7.0	5.0–6.5
Specific gravity	1.016	1.015–1.025
Protein	Negative	
Glucose	Negative	
Ketones	Negative	
Billirubin	Negative	
Urobilinogen	Normal	
Nitrite	Negative	
Blood cells	Negative	

ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; AFP, alpha-fetoprotein; BASO, basophil count; Ca2+, calcium; EOS, eosinophile count; FSH, follicle-stimulating hormone; fT3, tiiodothyronine; fT4, =thyroxine; HCG-β, β-subunit of human chorionic gonadotropin; $HCO3^-$=, bicarbonate; HCT, hematocrit; HGB, hemoglobin; IGF-1, insulin-like growth factor 1; K^+, potassium; LH, leutinizing hormone; LYM, lymphocyte count; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; MONO, monocyte count; Na^+, sodium; NEU, neutrophil count; O2Sat, oxygen saturation; PLT, platelet count; pO2, oxygen partial pressure; pCO2, carbon dioxide partial pressure; RBC, red blood cell count; TSH, thyroid-stimulating hormone; WBC, white blood cell count.

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Investigation

The patient was in good general condition during admission to the Department of Lung Diseases and Tuberculosis. The oxygen saturation was 97% breathing atmospheric air. No significant deviations from the norm, except a subcutaneous nodule of the left elbow fossa, were found in the physical examination. Mild hypocapnia was observed in arterial blood gases (Table 1). Other laboratory tests were insignificant, including serum angiotensin-converting enzyme (ACE) level and calcium metabolism (Table 1).

Small nodular opacities in the right subclavian area were observed in the chest X-ray (Fig. 1). However, high-resolution CT (HRCT) showed many nodular densities in the upper and middle zones of the right lung with central granular calcifications. The distribution of nodules was peribronchial, perivascular, and subpleural along the interlobar horizontal and oblique fissure. Moreover, a single nodule of 10 mm in the upper right lobe was observed (Fig. 2).

Pulmonary function tests (PFTs), including spirometry, lung volumes, and diffusing capacity for carbon monoxide, only verified an increase in functional residual capacity (FRC) (Table 3). The 6-minute walk distance was normal (700 m).

Sinus rhythm was observed on the ECG with a heart rate of 69 bpm and Q waves in leads II, III, and aVF.

Flexible bronchoscopy (FB) with bronchoalveolar lavage (BAL) of the middle lobe showed bilateral chronic bronchitis with dilated mucous vessels. An increased percentage of lymphocytes (35%) was verified in the bronchoalveolar lavage fluid (BALF). During hospitalization, transbronchial lung biopsy (TBLB) was also conducted. Histologic examination of collected lung tissue showed subepithelial discrete ('sarcoid-like') granulomas with multinucleated giant cells and epithelioid histiocytes surrounded by a thin rim of fibroblasts (histologic appearance may suggest sarcoidosis) (Fig. 3).

Ziehl–Neelsen staining, cartridge-based nucleic acid amplification test, and sputum and bronchial wash culture ruled out *Mycobacterial* infection. The interferon-gamma release assay was also negative.

Moreover, a core needle biopsy of the subcutaneous nodule of the left elbow fossa was conducted due to the suspicion of cancer. Many clusters of histiocytes, macrophages, and giant multinuclear cells with granuloma formation were observed in the aspirated sample (Fig. 4).

The ophthalmological examination exhibited no abnormalities.

MRI of the brain showed a pituitary gland size of 9 × 8 × 6 mm (anterior–posterior (AP) × right–left (RL) × head–foot (HF)). The contrast enhancement of the glandular lobe with a slightly irregular upper margin was visualized. The nerve lobe was invisible (Fig. 5).

Fluorine-18-fluorodeoxyglucose PET-CT (FDG PET-CT) was conducted to evaluate the development of the other organs. The hypermetabolic activity was visualized in the lungs, thoracic and pelvic lymph nodes, and left hip bone (SUVmax = 3.7) (Fig. 6).

Treatment

Treatment with prednisone (40 mg daily) was started. The desmopressin dose was reduced from 120 to 30 mg twice daily.

Outcome and follow-up

The resolution of DI symptoms was attained. The total duration of glucocorticosteroid (GCS) treatment is planned for at least 1 year.

Discussion

Sarcoidosis, like a chameleon, can mimic various diseases and involves several systems (4, 8). The diagnosis of BBS disease is complex and needs a consistent clinical picture supported by typical radiological findings and validated by histological noncaseating granulomas in the affected organs (2, 3, 4, 8). The clinician should actively examine

Table 2 Water deprivation test.

Urine sample – hours after onset of the test	**Urine specific gravity**	**Urine osmolality** (mOsm/kg)
2 h	1.004	144
4 h	1.004	143
6 h	1.004	161
8 h	1.005	262
After 2 µg of i.m.desmopressin	1.016	710
Normal range	1.015–1.025	50–1200

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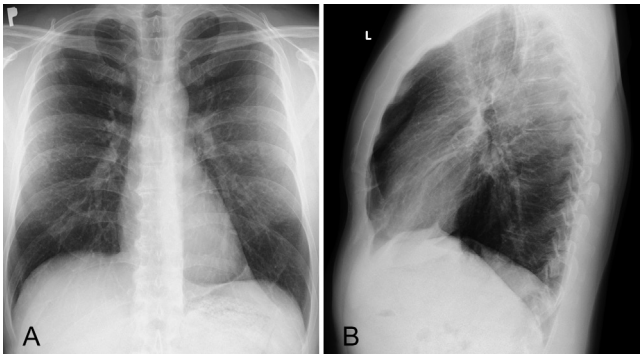

Figure 1
Chest X-ray (A, posterior–anterior projection; B, lateral projection). Small nodular opacities in the right subclavian area.

the different symptoms of the disease, initially and over time (1, 9).

The most frequently reported clinical manifestation of BBS disease is related to the respiratory system (1, 2). Lung imaging plays an important role in sarcoidosis. Chest X-ray and HRCT, depending on the disease stage, may show bilateral hilar or mediastinal lymphadenopathy, small nodules localized in the peribronchial, perivascular, and subpleural area, especially in the middle and upper zones, consolidations, and pulmonary fibrosis with extensive deformation of the lungs, axial traction bronchiectasis, and honeycombing (1, 2).

Comprehensive pulmonary evaluation of sarcoidosis also includes the results of PFTs (in particular with restrictive patterns), arterial blood gasometry, and FB (1, 2). During bronchoscopy, endobronchial biopsy of mucosal lesions or TBLB can be conducted and, most of all, endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) of the mediastinal lymph nodes (2). As a safe and reliable method, EBUS-TBNA allows the visualization of mediastinal structures and the collection of lymph node samples for histological examinations (2). Recently, cryobiopsy has also become a frequently used endoscopic tool for diagnosing interstitial lung diseases (2). Additionally, BAL and BALF analyses may increase the diagnostic yield of BBS disease. An elevated BAL lymphocyte count >15% and CD4:CD8 T cell ratio >4 support the diagnostic procedure (2). It is worth remembering that BALF lymphocytosis is not specific to BBS disease. It is also observed under other conditions (2). The presence in the history of exposure to occupational or environmental factors (e.g. beryllium, organic dust) and other systemic granulomatous diseases (e.g. tuberculosis) significantly complicates the diagnosis of pulmonary sarcoidosis (3).

In our patient's chest HRCT, typical pulmonary sarcoidosis findings were found. Additionally, there were mild hypocapnia in arterial blood gas analysis, an increase of FRC in PFTs, and lymphocytosis (35%) in the BALF analysis. The results of these studies brought us closer to sarcoidosis diagnosis. Moreover, the patient did not report occupational or environmental exposure to interstitial lung disease.

Once the pulmonary sarcoidosis is verified, other organ involvement should be analyzed (1, 2). Biopsy of the most suspicious lesions should be conducted in the event of sarcoid-related symptoms. Skin eruptions, subcutaneous nodules, palpable lymph nodes, enlarged parotid gland, lacrimal gland, or specific other ocular lesions are appropriate for sampling (1, 2).

Histological examination of the obtained samples shows the BBS disease when sarcoid granulomas formed by macrophages, epithelioid cells, multinucleated giant cells, and T and B lymphocytes are present (2, 7).

In the described patient, samples for histological examination were obtained from the subcutaneous nodule and pulmonary parenchyma. The granulomas were found in the collected samples.

PET and CT with FDG PET-CT is a sensitive technique for assessing sarcoidosis and the extent of disease and monitoring of therapeutic response in complex cases (1, 2). FDG PET-CT is especially recommended in patients with unexplained symptoms from other systems unrelated to organ involvement already verified by biopsy and for detecting a diagnostic biopsy site (1).

Our patient's FDG PET-CT images indicated hypermetabolic activity in the lungs, thoracic and pelvic lymph nodes, and the respiratory and skeletal systems.

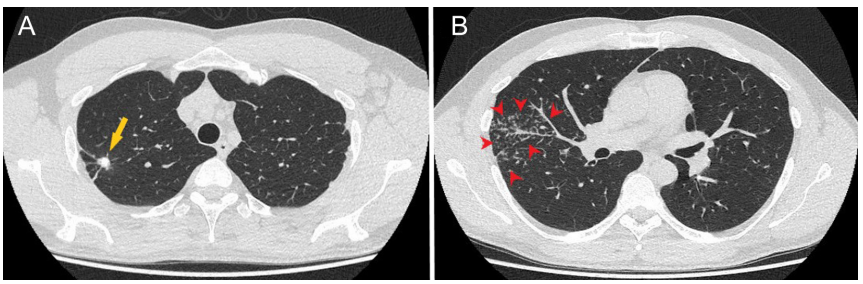

Figure 2
High-resolution CT. (A) A single nodule of size 10 mm in the upper right lobe (yellow arrow). (B) Many nodular densities in the right lung. The distribution of nodules is peribronchial, perivascular, and subpleural along the interlobar horizontal and oblique fissure (red arrowheads).

Table 3 Pulmonary function tests.

Parameter	Result	LLN	% predicted	*Z*-score
FEV1 (L)	4.3	3.77	90	−0.77
FVC (L)	5.78	4.75	97	−0.24
FEV1/FVC (%)	74.35	69.93	93	−0.98
FRC (L)	4.79	2.65	132	1.91
RV (L)	1.58	1.4	76	−1.22
TLC (L)	7.38	6.71	94	−0.68
RV/TLC (%)	21.35	20.19	73	−1.43
DLCO	9.94	9.85	82	−1.58

DLCO, diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin); FEV1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced vital capacity; LLN, lower limit of normal; RV, residual volume; TLC, total lung capacity.

The water deprivation test should be theoretically sufficient to identify the DI type (11). Unfortunately, polyuric–polydipsic states can show substantial overlap, making the diagnosis more challenging. A plasma copeptin level can accurately distinguish different forms of polyuria–polydipsia syndromes. A value of <2.6 pmol/L shows complete central DI with 95% sensitivity and 100% specificity. Additionally, the measurement of plasma copeptin level in conjunction with hypertonic saline infusion test can increase the diagnostic yield of the differential DI diagnosis (11). In clinical practice of sarcoidosis management, biomarkers, such as serum ACE levels and calcium metabolism, indicate active inflammation and responsiveness to treatment (2, 8).

In the reported case, the water deprivation test was confirmed in the described patient central DI. Other laboratory tests, including ACE and calcium metabolism, were normal.

NS may be confined to the nervous system or occur with other symptoms and signs of a multisystem disease (8, 10). NS diagnosis is difficult, especially when the neurological localization of the disease is not accompanied by other characteristics of systemic localization (4, 8). MRI

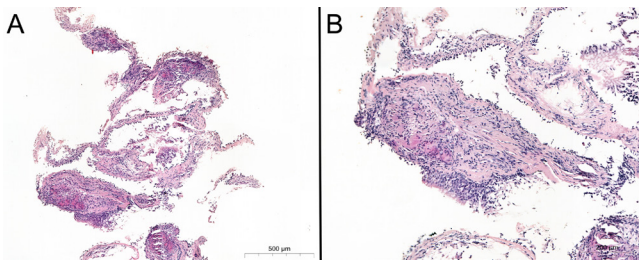

Figure 3
Transbronchial lung biopsy. Hematoxylin–eosin stain. (A) magnification 100×, (B) magnification 200×; subepithelial discrete ('sarcoid-like'') granulomas with multinucleated giant cells and epithelioid histiocytes surrounded by a thin rim of fibroblasts.

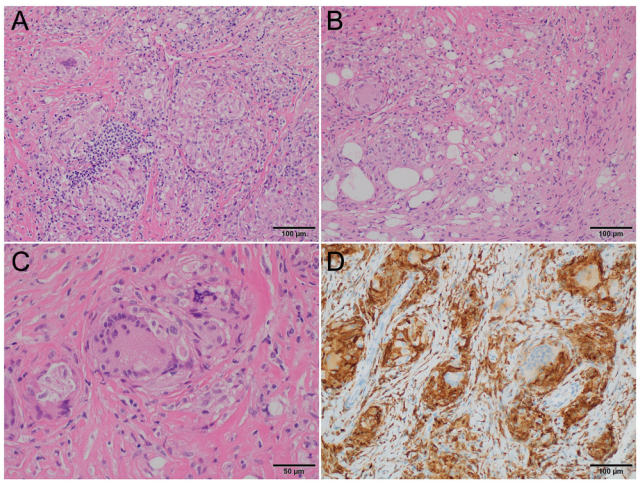

Figure 4
Core needle biopsy of the subcutaneous nodule of the left elbow fossa. Sarcoidosis involving the deeper layers of the subcutaneous tissue with the presence of multiple granulomas, Langhans giant cells, and focal inflammatory infiltration from reactive lymphocytes (A); visible infiltration of adipose tissue with its focal necrosis (B); the Langhans giant multinuclear cell (C); strong positive immunohistochemical reaction with CD163 marking macrophages/histiocytes forming granulomas (D).

is the gold standard for imaging in NS diagnosis (1). In cases of central DI, MRI of the sellar and suprasellar regions with gadolinium should be obtained. The absence of hyperintensity on T1 images ('bright spot') in the posterior pituitary can show an absence of posterior pituitary function (11). Nerve tissue can be difficult to access for histological NS examination. Therefore, multiorgan diagnostics and the exclusion of other potential causes of symptoms are of key importance in NS (8). Cerebrospinal fluid (CSF) examination is considered highly sensitive and relatively specific for assessing NS. Elevated protein level and increased lymphocytes count T CD4+/T CD8+ ratio to above 3:1 suggest NS (4, 8, 10).

In the described case, an MRI of the brain presented the absence of 'bright spot' sign and contrast enhancement of the pituitary glandular lobe. CSF examination was not conducted because of the patient's lack of consent to the lumbar puncture.

NS's most common clinical manifestation is a unilateral or bilateral facial nerve disorder. Sarcoid-induced optic neuropathy, impairment of the cranial nerves innervating extraocular muscles (III, IV, and VI), vertigo, deafness, dysphagia, dysarthria, headache, many intracranial masses, meningitis, subarachnoid or intraparenchymal hemorrhage, ischemic strokes, and peripheral neuropathy are also reported (5, 8, 10). Endocrine manifestations of sarcoidosis resulting from dysfunction of the hypothalamic–pituitary axis include DI, amenorrhea,

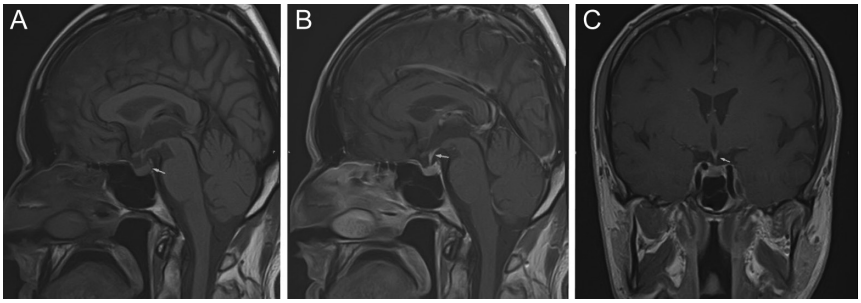

Figure 5
Brain magnetic resonance (A and B, sagittal scan; C, axial scan). Pituitary gland size 9 × 8 × 6 mm (AP × RL × HF). (A) T1-weighted without contrast-enhanced image indicates the absence of 'bright spot' sign in the posterior pituitary (blue arrow). (B and C) T1-weighted contrast-enhanced image indicates the contrast enhancement of the pituitary stalk with a thickening of the upper basal part (blue arrows).

galactorrhea, hyperprolactinemia, or panhypopituitarism (5, 8). DI secondary to sarcoidosis is a consequence of direct destruction of the hypothalamic osmoreceptor or injury/infiltration of the supraoptic structures (5, 8).

Based on multifaceted diagnostics, pulmonary and extrapulmonary sarcoidosis was diagnosed. In the described patient, endocrine dysfunction of the hypothalamic–pituitary axis was the first sign of NS and multiorgan sarcoidosis. No other neurological signs were observed.

In the case of patients with biopsy-proven sarcoidosis and without evidence of an alternative diagnosis, the next step in clinical management is to assess the indications for treatment (1, 3).

Therapeutic decisions need assessment of organ involvement and damage, the risk of significant morbidity, and the effect on the quality of life of the disease and treatment (3, 9). The efficacy of sarcoidosis treatment depends on the stage of the disease, the involvement of extrapulmonary organs, and the intensity of the inflammatory process (8). The initiation of the therapy is shown in the case of clinically significant involvement and/or damage to the heart, eye, CNS, and progressive symptomatic lung disease (3, 9). Patients with pulmonary sarcoidosis without lung function impairment and radiological progression do not need treatment.

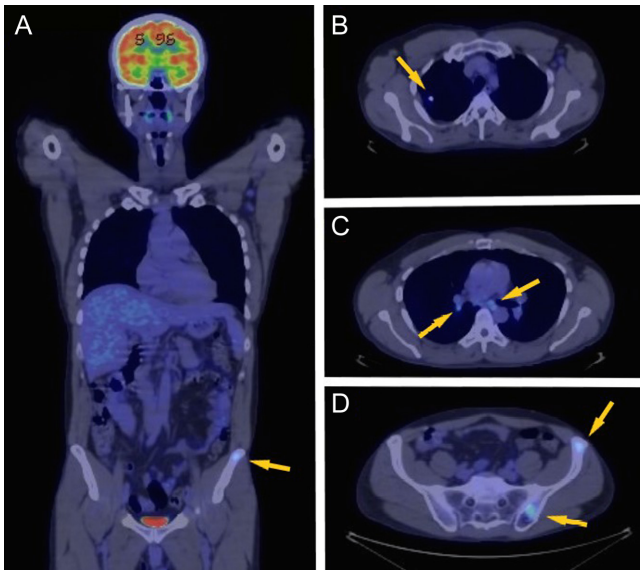

Figure 6
Fluorine-18-fluorodeoxyglucose PET-CT (A, coronal scan; B, C and D, axial scans). Hypermetabolic activity in the lungs, thoracic and pelvic lymph nodes, and left hip bone (yellow arrows).

GCSs remain the first-line treatment for sarcoidosis (3). The duration of maintenance therapy is based on the drug efficacy and the balance of side effects (3, 9). However, for courses shorter than 1 year, an increased risk of relapse has been reported (3).

Other immunosuppressants such as methotrexate, cyclosporine A, infliximab, adalimumab, azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine, and rituximab may be used alone or combined with GCS for sarcoidosis treatment, especially in patients who are not responding to the single-drug regimen with corticosteroids (9, 10). The severe side effects associated with their use also demonstrated the need to modify the therapy (8, 9).

To establish an individual treatment plan for multiorgan sarcoidosis, a patient's opinion, involvement of appropriate specialists, and multidisciplinary discussions are recommended (1).

A thorough systemic DI assessment allowed the identification of the real cause of endocrine disorders in a described patient. A diagnosis of multiorgan sarcoidosis was made, and GCS therapy was initiated. Treatment was well tolerated, and the resolution of endocrine symptoms was attained.

The clinical course of NS is difficult to predict (4, 8, 10). Signs of hypothalamic–pituitary sarcoidosis may be permanent, but the spontaneous resolution of symptoms has also been reported, similar to the self-limited natural course of BBS pulmonary disease (8). Available literature reports propose that GCS and/or immunosuppressive therapy of NS involving the hypothalamic–pituitary region could not restore the function of the anterior pituitary gland or improve DI. Therefore, simultaneous supportive

hormonal treatment for pituitary insufficiency should be implemented (8, 9).

A case of DI secondary to multiorgan sarcoidosis was presented. Based on our experience, the importance of a multifaceted differential diagnosis of DI in determining the best therapeutic option for the patient was emphasized.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Author contribution statement
K G and Ł M contributed equally to the manuscript. All authors read and approved the final version of the manuscript and ensure this is the case: K G, Ł M, R M M, A P P, and A C S analysed and prepared the data, wrote the manuscript; K G was the leading doctor; Ł M and R M M was involved in the clinical management of the patient; A P P and A C S performed histopathological examinations.

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