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Disseminated lichenoid type cutaneous sarcoidosis: a challenge to diagnose and manage

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ABSTRACT

Sarcoidosis is a rare chronic inflammatory disease of unknown origin that can affect multiple organs of the body to a varying extent and degree. It seems to be provoked by an immune reaction to different triggers, such as infections, dust or chemicals. Sarcoidal skin involvement is the second most common manifestation of sarcoidosis, respiratory system being the most common. Ocular involvement appears even rarer. To our knowledge, there is scarce evidence of combined cutaneous and ocular sarcoidosis, sparing respiratory system. For this reason, we share a case of 79-year-old male with widespread abrupt cutaneous sarcoidosis sparing the lungs. This case illustrates that in cases of first- line treatment failure and patient's comorbidities that limit the choice of second-line treatment, phototherapy could be applied. Combined UVA and UVB (COMBI) phototherapy is as effective as UVA1 phototherapy.

Keywords: sarcoidosis, skin, phototherapy.

Introduction

Sarcoidosis is a rare chronic inflammatory disease of unknown origin that can affect multiple organs of the body to a varying extent and degree (1–4). It is a granulomatous disease, characterized by presence of noncaseating epithelioid granulomas in organs and tissue, such as the skin, lung, lymph nodes, eyes, joints, brain, kidneys, and heart (5). Although the exact cause of sarcoidosis remains unknown, it seems to be provoked by an immune reaction to different triggers, such as infections, viruses, bacteria, dust or chemicals (4). Various associations have been described, including occupational and environmental exposures to beryllium, autoimmune disorders (e.g., autoimmune thyroid disorders), and microorganisms like mycobacteria and propionibacteria (4,6). In the majority of cases, sarcoidosis typically affects lungs and presents as bilateral hilar lymphadenopathy and reticular opacities in lungs. Nearly 90- 95% of patients have some pulmonary involvement (7). Sarcoidal skin involvement is estimated to occur in approximately 25-30 % of patients ant it is the second most common manifestation of the disease (8). Sarcoidal skin lesions are classified into specific and nonspecific based upon histopathologic findings. Specific skin lesions, that occur in 9- 36% of patients, contain noncaseating epithelioid granulomas, which represent the classic histopathologic findings in lesional tissue. All other cutaneous findings associated with sarcoidosis are categorized as nonspecific. Sarcoidosis confined only to skin is quite uncommon; it accounts only for 4-5 % of all sarcoidosis cases (9). Because lesions present in a vast variety of morphologies, cutaneous sarcoidosis is known as one of the "great imitators" in dermatology (1). Ocular involvement is rarer and occurs in up to 25% of patients with sarcoidosis. It is the presenting phenomenon in 5% of all sarcoidosis cases (11). To our knowledge, there is scarce evidence of combined cutaneous and ocular sarcoidosis, sparing respiratory system. For this reason, we share a case of widespread abrupt cutaneous sarcoidosis without systemic involvement.

Case report

A 79-year-old Caucasian male with multiple chronic medical conditions was admitted to Vilnius University Hospital Santaros Klinikos with a 6-month history of disseminated, mildly to moderately pruritic skin rash affecting the whole body area. Two weeks before the rashes appeared, the patient had been vaccinated against influenza. At the beginning of the disease, the rash appeared on the chest, and then proceeded to spread to arms, abdomen and dorsal region of torso. After a week, oedema of periorbital region, eyelids and lips appeared. Then, conjunctivae of both eyes turned red. In the following month, a fever of up to 38.4°C started and continued for 5 days. The patient was admitted to the Infectious disease unit where diagnosis of multiform exudative erythema was made. Treatment consisted of oral prednisolone (25 mg twice a day (b.i.d.) for 8 days), infusion therapy of sol. Ringer 500 ml intravenously, gutt. Dexamethasone every 4 hours (g4h), and continuous treatment of concomitant chronic conditions. Temporary improvement was observed and the patient was discharged from the hospital after 8 days. The patient was guided to continue taking oral prednisolone 20 mg b.i.d., gradually reducing the dosage until complete termination of oral steroid intake. In addition, a referral to an allergologist was made. The relapse happened 2 weeks after completion of oral steroid therapy. The patient was referred to a dermatologist. The histopathological investigation showed granulomatous skin disease, most probably of sarcoidal origin. The patient was admitted to the Dermatovenereology unit for detailed examination and treatment. Ocular lesions were evaluated by an ophthalmologist and diagnosis of chronic blepharitis, of probable sarcoidal origin, was made. Treatment consisted of emollients b.i.d., topical betamethasone q.d., gutt. Dexamethasone gh4 and continuous treatment of concomitant chronic diseases. Hospitalization lasted for 6 days and significant improvement was observed. The patient was referred to a pulmonologist for respiratory system evaluation. He was also instructed to continue the administered treatment on a daily basis. Repeated admission to a Dermatovenereology unit was

scheduled after 1 month, following the examination by the pulmonologist.

Past medical history was notable for numerous cardiovascular conditions: aortic valve stenosis (managed by biologic aortic valve replacement), arterial hypertension, premature ventricular complexes, heart failure NYHA class III (controlled by taking tab. Nebivololi 5 mg. and tab. Quinaprili 10 mg). In addition, the patient had chronic autoimmune thyroiditis, for which tab. Levothyroxine 75 mcg was taken daily. Moreover, a hormonally inactive incidentaloma of left adrenal gland was present. In the childhood, primary pulmonary tuberculosis was diagnosed.

Physical examination revealed widespread, violaceous to erythematous papules with shiny surface and hyperpigmented borders, ranging 2 – 10 mm in diameter. Most of the lesions were distributed on the trunk, shoulders and extremities (Figure 1a, Figure 1b). Lesions mimicked lichen planus and were mildly itchy. Nonetheless, further histopathologic analysis of skin lesions revealed noncaseating epithelioid granulomas located in derma. In addition, nonspecific ocular involvement was observed.

The patient denied shortness of breath, chest tightness, dyspnea, and chest, joint or muscle pain. Despite the fact that skin lesions occurred all over the body, facial involvement was minimal. However, ocular redness, itching, minor swelling of eyelids and general fatigue accompanied cutaneous symptoms (Figure 2a, Figure 2b). On examination, the vital signs were normal. Detailed clinical examination revealed no palpable lymphadenopathy or other signs of internal abnormalities.

Performed laboratory tests revealed peripheral monocytosis, slightly increased count of immature granulocytes, iron deficiency anemia, elevated levels of C- reactive protein, increased erythrocyte sedimentation rate, markedly elevated levels of thyroid- stimulating hormone and slightly increased levels of uric acid. Other laboratory parameters were within normal ranges (Table 1). Urinalysis was also within normal ranges.

On the chest X-ray fibrotic pulmonary changes and insignificant hilar lymphadenopathy were present. Chest CT-scan revealed petty paravertebral, apical and subpleural changes. In addition, no signs of inflammatory infiltration, focal consolidation or masses were detected. Spirometry was within normal ranges. Detailed pulmonary examination denied the presence of pulmonary as well as systemic sarcoidosis. Visualized pulmonary changes were considered as residual phenomena from primary pulmonary tuberculosis in childhood.

Second evaluation by ophthalmologist revealed episcleritis of both eyes, of possible sarcoidal etiology. However, intense inflammatory reaction put obstacles to thorough examination.

Repeated histopathologic findings showed slight epidermal hyperkeratosis, clear-bordered and in some places confluent epithelioid granulomas in derma, which were insignificantly surrounded by monomorphonuclear cells (Figure 3a, Figure 3b). No signs of lichen planus or malignancy were observed.

The results of clinical, laboratory, radiographic, and histopathologic examination were consistent with the diagnosis of cutaneous sarcoidosis, disseminated lichenoid type. Ophthalmologic examination did not contradict the plausibility of ocular lesions to be of sarcoidal etiology.

Treatment with topical steroids was initiated. First line treatment was Betamethasone valerate ointment b.i.d, later changed to Clobetasol propionate ointment b.i.d. due to poor cutaneous response. Furthermore, prednisolone eye drops three times a day (t.i.d.), emollients with zinc b.i.d and treatment of comorbidities were administered. The dosage of levothyroxine was increased to 100 mcg per day. After 3 weeks, the patient reported improvement of ocular condition, but skin lesions did not resolve completely. Due to slow response to topical therapy, the treatment was combined with 7 sessions of COMBI phototherapy for full body. Following 2 weeks of combined treatment, skin infiltration and erythema subsided noticeably, the rash stopped spreading and post-inflammatory hyperpigmentation appeared. The patient received additional COMBI

phototherapy and resumed topical steroid therapy at the day hospital. After 18 sessions of COMBI phototherapy with a total dose of 23.050 J/cm2 of UVA1 and 14.200 J/cm2 of UVB, only post-inflammatory hyperpigmentation was observed. The patient was recommended to continue daily application of emollients and to repeat laboratory and radiologic tests on a regular basis to rule out any signs of probable development of systemic sarcoidosis (Figure 4a, Figure 4b).

Discussion

Skin manifestations of sarcoidosis occur in up to 30% of cases (12). While pulmonary sarcoidosis is the most prevalent manifestation of the disease, involvement of the skin is the most common extrapulmonary presentation of this condition (13). Moreover, it mainly occurs at the onset of the disease (14). Cutaneous sarcoidosis lesions are classified into specific and non-specific ones based upon histopathological findings. Specific lesions contain sarcoidal granulomas, and non-specific lesions are reactive processes. Common specific sarcoidosis skin lesions appear as maculopapules, nodules, plaques, subcutaneous nodules, infiltrative scars and lupus pernio. Most common non-specific skin lesions are erythema nodosum, multiform erythema, calcifications and prurigo (14). As this clinical case illustrates, the first skin lesions were considered as a symptom of exudative multiform erythema. According to the medical records, the diagnosis was made only by the history of the eruption and clinical findings. Unfortunately, at that time no skin biopsy was performed. Although temporarily, the disease responded well to oral prednisolone until the therapy was finished. The most common type of granulomatous cutaneous involvement in sarcoidosis is maculopapular eruption, which can be only slightly infiltrated, with little epidermal change, usually red-brown to purple and less than 1 cm in diameter. They are commonly seen on the face, particularly on the eyelids, around the orbits, and in the nasolabial folds, although the occipital area of the neck, trunk, extremities, or even mucous membranes may be involved (15). Our patient presented with widespread, violaceous to erythematous papules with shiny surface and hyperpigmented borders, ranging 2- 10 mm in diameter. Most of the lesions were distributed on the trunk, shoulders and extremities. Although facial involvement was minimal, eye redness, itching and minor swelling of eyelids were prominent. Our clinical findings visually resembled cutaneous lichen planus. However, histopathologic examination revealed noncaseating epithelioid granulomas in derma. The lichenoid form of sarcoidosis is classified as specific skin lesions. This extremely rare skin manifestation of the disease occurs in 1%-2% of cutaneous sarcoidosis cases (16). Clinically, the lichenoid type presents as multiple 1-3 mm, erythematous or violet maculopapular lesions, covered with fine squams. Most commonly, rashes distribute on face, extensor areas of limbs and trunks. The dermoscopy usually reveals circular or oval yellowish-brown lesions with the absence of Wickham‘s striae, even if this pattern is not specific for sarcoidosis. These homogeneous patches indicate for a granulomatous skin disease. Lichenoid lesions have often been reported in combination with ocular and joint complications, but respiratory system involvement is usually absent (16), as our case demonstrates.

Sarcoidosis confined only to skin is quite uncommon; it accounts only for 4-5 percent of all sarcoidosis cases (9). We performed thorough clinical, laboratory and radiologic examination to rule out the involvement of other major organ systems. Chest CT scan ruled out pulmonary involvement of the disease. This supports Mangas et al., since no association between the type and spreading of lesions and systemic involvement in sarcoidosis has been demonstrated with the exception of erythema nodosum that often resolves spontaneously (14).

Ocular involvement occurs in 25–50% of patient with systemic sarcoidosis, with conjunctival granulomas, lacrimal gland involvement and uveitis being the most common manifestations (17). Although less common, the orbit and ocular adnexa are involved in 10% of patients with systemic sarcoidosis and 27% of patients with ocular sarcoidosis (17). As far as the present case is concerned, ophthalmologic evaluation revealed episcleritis of both eyes, of possible sarcoidal

etiology. According to Pasadhika et al, scleritis is uncommonly associated with sarcoidosis, but sarcoidosis should be considered in the differential diagnosis of scleritis. Sarcoidosis-associated scleritis is more likely to be non-necrotizing, and tends to respond well to oral corticosteroids (18). As this case illustrates, ocular condition improved noticeably, when Dexamethasone eye drops were applied.

Performed laboratory tests and their findings, i. e. increased erythrocyte sedimentation rate and elevated levels of C-reactive protein support the fact that sarcoidosis is an inflammatory disease (19). Monocytosis in the bloodstream is also a common finding in majority cases of sarcoidosis (20,21). Other hematological abnormalities in sarcoidosis, although less often reported, may include mild anemia, neutropenia, eosinophilia and thrombocytopenia (21).

It is well known that sarcoidosis can be provoked by an immune reaction to different triggers, such as infections or chemicals. Moreover, the disease is associated with autoimmunity such as autoimmune thyroid disorders (AITDs) (4). In childhood, the patient was diagnosed with primary pulmonary tuberculosis. To this day, chest X-ray and chest CT-scan show changes of pulmonary structure, which might be remaining phenomenon of the past infection. The role of mycobacteria in the etiology of sarcoidosis has been extensively studied. Several studies using immune assays and the isolation of antigens (e.g. Mycobacterial catalase-peroxidase antigen, mKatG) revealed that mKatG might lead to a T-cell response, which leads to formation of granulomas and might therefore be a pathogenic antigen (22). The balance of evidence favors mycobacteria or their products as a trigger for inciting immune responses leading to sarcoidosis in a proportion of patients, which is likely to be higher in countries with high tuberculosis burden (22). To illustrate this point, The World Health Organization (WHO) placed Lithuania among the high TB burden countries (23).

The association of sarcoidosis and thyroid autoimmunity has been reported by several studies (24). Our patient was diagnosed with chronic autoimmune thyroiditis several years ago, prior to the manifestation of cutaneous sarcoidosis. Although on admission day levels of anti-TPO were low, it is estimated that 5 % of patients with a diagnosis of Hashimoto's thyroiditis have no measurable thyroid antibodies (25). Increased levels of TSH suggested poor control of thyroid disease. From the first day of admission, we increased the dosage of levothyroxine from 75 mcg daily to 100 mcg, believing that this will improve the general condition of the patient.

Treatment protocol mainly consisted of topical corticosteroids and skin maintenance therapy. Corticosteroids are the worldwide-accepted standard treatment of sarcoidosis (26). Local superpotent corticosteroids applications to the skin lesions under occlusion once or twice daily are recommended (26). Other treatment options include systemic steroids, methotrexate, antimalarial agents, tetracycline derivatives (26). Concomitant chronic diseases limited additional drug therapy in our case. To accelerate a slow response to steroid therapy, we started COMBI phototherapy. However, data on the effect of phototherapy on cutaneous sarcoidosis are scarce. There are some cases reported where treatment with UVA-1 (340 to 400 nm) light was associated with improvement in cutaneous sarcoidal lesions because of its immunomodulatory effect (27,28). This clinical case showed significant result of COMBI phototherapy with remains of post-inflammatory hyperpigmentation only.

Although cutaneous sarcoidosis, sparing lungs and other major organ systems, occurs very rare, it is crucially important to recognize it, because skin lesions may lead to diagnosis of pulmonary disease. Almost every treatment method is based on limited data. Topical steroids are agents of the first choice. In cases of treatment failure and comorbidities, when second-line treatment is of limited use, phototherapy can be initiated. Our case demonstrated that COMBI phototherapy is as effective as UVA1 phototherapy.

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Table 1. Laboratory data.

Variable	Reference range (adults)	On admission
White cell count (*10e9/l)	4- 9.8	9.39
Differential count (%):		
Neutrophils	40- 65	52.3
Lymphocytes	25- 37	30.8
Monocytes	2- 10	16.6
Eosinophils	0-5	0.2
Basophils	0-1	0.1
Immature granulocytes	0-0.9	2
Differential count (*10e9/l):		
Neutrophils	1.5-6.0	4.91
Lymphocytes	1.0-4.0	2.89
Monocytes	0.1-0.9	1.56
Eosinophils	0-0.7	0.02
Basophils	0-0.11	0.01
Immature granulocytes	0-0.09	0.19
Erythrocyte count (*10e12/l)	4.3-5.8	4.29
Hematocrit (l/l)	0.4-0.48	0.38
Hemoglobin (g/l)	128- 160	116
Mean corpuscular volume (fl)	78-96	90
Mean corpuscular hemoglobin (pg)	26-31	27
Mean corpuscular hemoglobin concentration (g/l)	310-370	301
Platelet count (*10e9/l)	140- 450	225
Erythrocyte sedimentation rate (mm/h)	<=10	54
Glucose (mmol/l)	5.99	4.2-6.1
C reactive protein (mg/l)	<=5	34.6
Thyroid- stimulating hormone (mU/l)	0.4-4.0	6.756
Anti-Thyroid Peroxidase (kU/l)	<5,61	0
Creatinine (μmol/l)	62-115	73
Estimated Glomerular filtration rate (ml/min/1.73m^2)	>90	84
Potassium (mmol/l)	3.5-5.0	4.3
Sodium (mmol/l)	135-145	146
Chloride (mmol/l)	98-107	106
Ionized calcium (mmol/l)	0.98-1.13	1.04
Calcium (mmol/l)	2.15-2.55	2.29
Uric acid (μmol/l)	202-372	400
Anti-nuclear antibodies	<1:40	negative

Figure 1a

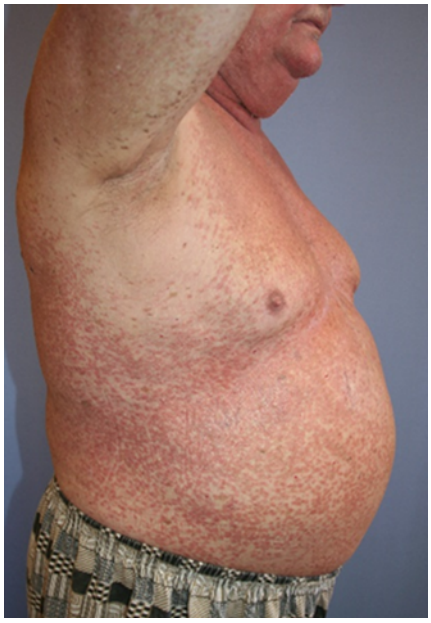


Figure 1b

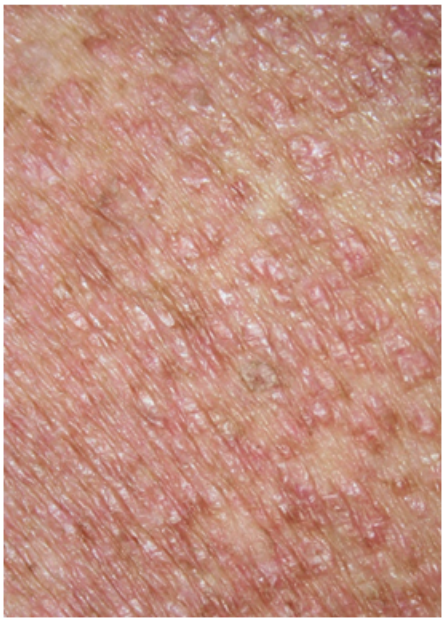


Figure 2a

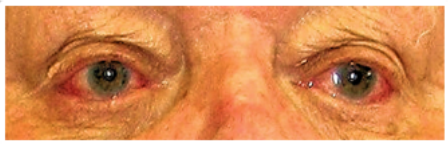


Figure 2b

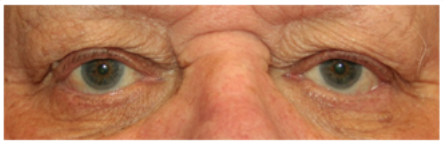
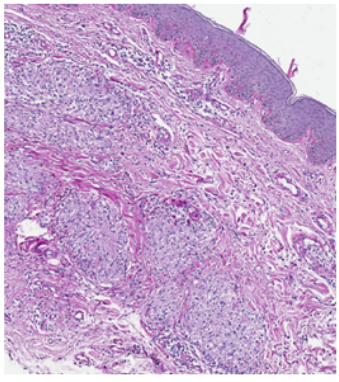


Figure 3a



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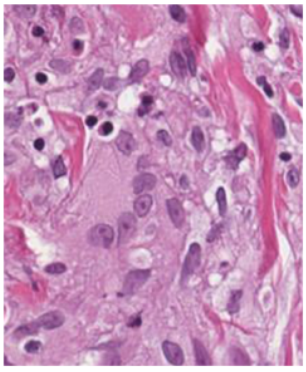


Figure 4a

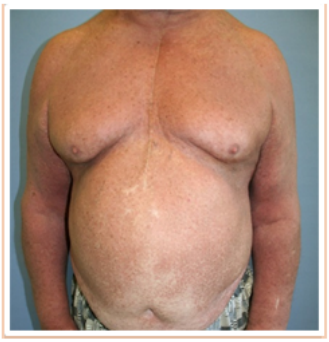
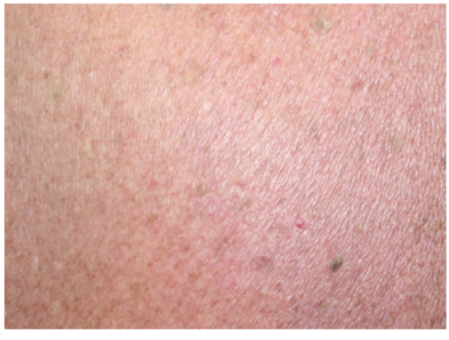


Figure 4b



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