The first reported case of erythrodermic sarcoidosis with systemic involvement during COVID-19 vaccination

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Abstract

Post-vaccinal and parainfectious activation of the immunity with subsequent development of a certain immunological/skin-immunological disease is not rare in clinical practice. This concept is mentioned in relation to molecular/antigenic mimicry. To this day, the pathogenesis of sarcoidosis and sarcoid-type reactions remains a mystery. Moreover, they can be a warning sign of changes in tissue homeostasis, whether they are infectious, non-infectious-immunological, tumor-related, *etc*. We present a rare form of erythrodermic sarcoidosis with massive systemic involvement (pericarditis, supraventricular tachycardia, hepatitis, iritis/iridocyclitis, pulmonary fibrosis/bihilar lymphadenopathy, and arthritis) developed after receiving the ChadOx1-S vaccine for COVID-19. Systemic immunosuppressive therapy with Methylprednisolone was introduced according to a scheme (in a reduction mode with an initial dose of 40 mg/day intravenously) in combination with topical Pimecrolimus 1% cream twice a day. Rapid improvement of the symptoms was observed within the first two days of treatment. According to the scientific literature, the presented patient turns out to be the first case of erythrodermic sarcoidosis (with systemic involvement), described as a side effect after vaccination and/or administration of a certain medicinal form.

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Introduction

The pathogenesis of sarcoidosis and sarcoid reactions remains in mystery. Despite the advances at the molecular level, the differentiation of these two conditions stays controversial and, in practice, is often impossible.[1]

The concept of sarcoidosis not having its own entity and favoring a sarcoid-type reaction is also largely due to the fact that disruption of tissue integrity, through the incorporation or invasion of various infectious or non-infectious (but still immunogenic) antigens, causes a uniform or monomorphic type of reaction, namely a sarcoid type of reaction.[1]

According to the hypothesis shared above, infections and vaccinations could be perceived as triggering factors, for both sarcoidosis and sarcoid-type reactions,[2] regardless of the sometimes-problematic nature of their classification.

Case Report

A 59-year-old woman reported to the Dermatology Department with primary complaints of a rash, that appeared over her whole body in August 2021 (Figures 1 and 2). Skin symptoms started after vaccination with the second dose of VAXZEVRIA/ChadOx1-S for COVID-19. Three vaccinations with VAXZEVRIA/ChadOx1-S were done in March, May, and November 2021. At the same time, the patient complained about severe pain in the shoulder joints and wrists, as well as the inability to raise the upper limbs above the horizontal. The reason for the hospitalization was to give a precise diagnosis and start proper therapy.

The dermatological examination during her last hospitalization showed a picture of suberythrodermia on the skin of the trunk, upper and lower limbs, and face. Erythematous-edematous confluent papules with follicular involvement are observed, in places with decent pityriasiform desquamation (Figures 1 and 2).

In February 2022, she was admitted to the Cardiology Department due to pericarditis and paroxysmal supraventricular tachycardia, treated with colchicine 0.5 mg two times a day, ibuprofen 800 mg once daily for 8 months, as well as short-term therapy with amiodarone hydrochloride (only within the inpatient stay), which was suspended in September 2022 due to complete remission.

In addition, hepatomegaly with transaminases five times higher than normal, fatty degeneration of the liver, and suspicions of possible autoimmune hepatitis within the framework of systemic involvement in sarcoidosis were found. Treatment with a hepatoprotector for two months was prescribed: ademetionine 500 mg twice a day with good response.

In March 2022, the patient was tested for hepatitis B and C, but markers came out negative; antinuclear antibody (ANA) screening 1:320 with a borderline result, ANA subtyping - negative, and quantiferon/TB Gold Quantiferon test also came out negative. At the same time, the patient underwent a skin biopsy. The pathohistological changes were similar to those of sarcoidosis.

In April 2022, a computed tomography scan of the torso was performed - bilateral axillary lymph nodes up to 6 mm, fibrous changes at the apex bilaterally with single nodules on the right /3 mm/, small calcifications mainly in the lower lung fields, mediastinal lymph nodes enlarged /6 mm/, pleural adhesions in the left basal, subsequently interpreted as stage 1 sarcoidosis.

In the same month, she was diagnosed and treated for iridocyclitis. Treatment continues since then with Chloramphenicol/Dexamethasone sodium phosphate 5 mL three times a day and ketorolac trometamol solution 5 mg/mL also three times a day.

Treatment for cutaneous sarcoidosis was started for the first time in May 2022 for 20 days with hydroxychloroquine sulfate 200 mg administrated two times a day, with a good initial response, but due to an occurred side effects, the therapy was discontinued.

In October 2022, three additional biopsies were performed in our department with the conclusion (Figure 2) that the histological constellation in all three biopsies was dominated by a sarcoid granuloma reaction, and the histological pictures corresponded to that of cutaneous sarcoidosis: orthohyperkeratosis horizontally alternating with parakeratosis, uniform acanthosis with elongation and confluence of the distal parts of the epidermal ridges, diffuse sarcoid granuloma band of epithelioid cells and lymphocytes with single Langhans-type giant cells in the upper and middle dermal segments (Figure 3).

Laboratory tests were done. The results were normal, except for the neutrophils – 43.1% (normal range 45-80%), rheumatoid factor – 16.1 IU/mL (normal range less than 15 IU/mL), blood sugar levels – 8.5 mmol/L (normal range less than 7.8 mmol/L).

After consultation with a rheumatologist and an X-ray examination of the affected joints, the diagnosis of rheumatoid arthritis was rejected, and the X-ray findings were interpreted more as a reactive form of arthritis within the underlying disease.

The anamnestic data, the clinical picture, the instrumental diagnosis, and the histopathological finding fully corresponded with the diagnosis of suberythrodermic sarcoidosis with joint, pulmonary, and eye involvement, which occurred after the second vaccination for COVID-19. The additional documentary data in favor of pericarditis and hepatitis were also interpreted as a transient involvement within post-vaccination-onset sarcoidosis, influenced beneficially by the short-term systemic chloroquine and long-term colchicine regimen.

Regarding ocular involvement, topical therapy was not changed during hospitalization.

Due to the currently available data on the active skin and pulmonary involvement, systemic therapy with methylprednisolone 40 mg/intravenous was started in a reducing regimen according to a scheme, which resulted in a visible relief of the joint pain and suberythrodermia already within the first two infusions. Topical

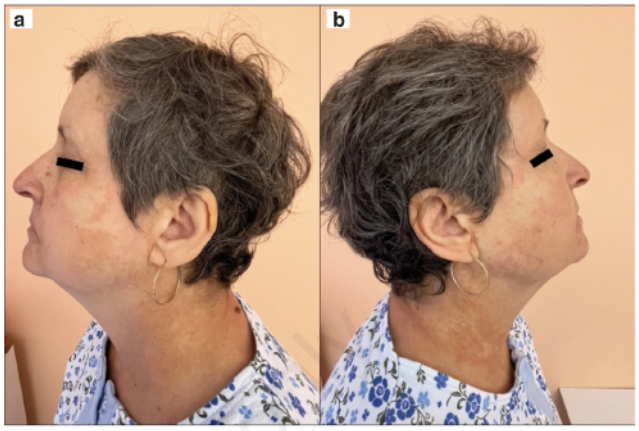

Figure 1. a,b) Small erythematous papules with follicular and parafollicular localization, confluating between each other, occupying the face, in the form of erythrodermia.

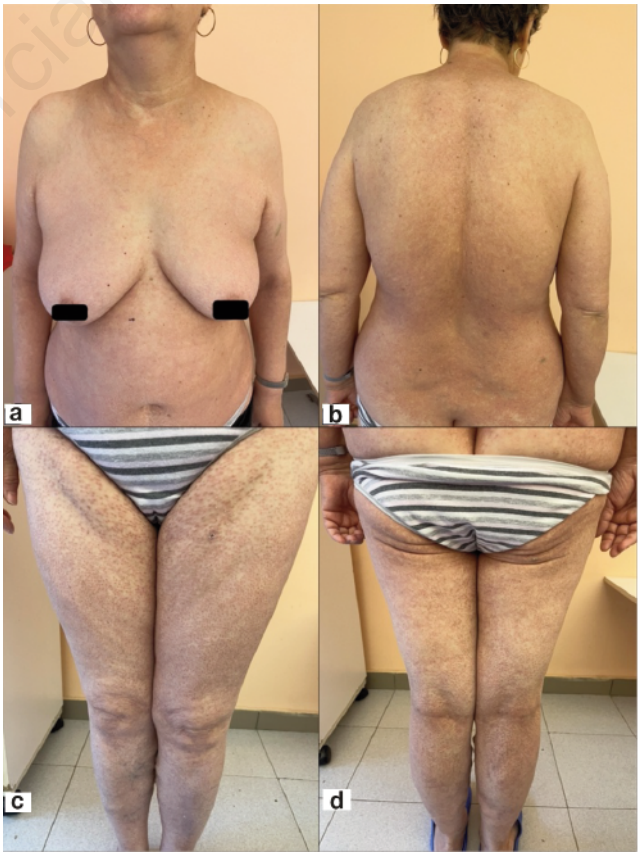

Figure 2. a-d) Small erythematous papules with follicular and parafollicular localization, confluating between each other, occupying the torso (a,b), upper (a,b), and lower (c,d) limbs, in the form of erythrodermia.

therapy was performed with Pimecrolimus 1% cream twice daily. The patient's outcome was successful as it showed no signs of suberythrodermia (Figure 4).

Therapy was changed, due to the occurrence of hypertension as a side effect to the previous therapy plan, to methotrexate 2.5 mg twice in the morning and twice in the evening and folic acid 0.4 mg once a day for six days, except the day when the patient takes the methotrexate.

Discussion and Conclusions

In the context of molecular mimicry,[3] the development of sarcoidosis after COVID-19,[4,5] or after/within vaccination for COVID-19,[6-10] should not be surprising and has been described repeatedly in the scientific literature.[4-10]

The leading connection in the molecular mimicry hypothesis, as a generator of a cross-mediated immune response in sarcoidosis/sarcoid-type reactions, appears to be the incorporation of both infectious/immunogenic (fresh COVID-19 infection) and the still immunogenic but non-infectious material (vaccination for COVID-19).[2,3]

The dilemma of whether the subsequently established sarcoid granulomas will be interpreted as an independent disease, sarcoidosis, or as a sarcoid-type reaction, remains unresolved in a high percentage of cases.[1,11]

According to Wigley and Musso (1951), who described a third case of a patient with erythrodermic sarcoidosis, the first case of erythrodermic sarcoidosis was registered in 1920 by Schaumann.[12]

It was only in 1948 that Lever and Freiman described in the Archives of Dermatology and Syphilology a second case of a patient with erythrodermic sarcoidosis.[13]

As a concept, erythrodermic sarcoid was mentioned for the first time in the medical literature in 1962.[14] The 5th case of erythrodermic sarcoidosis was described in a child in 1976 in the *British Journal of Dermatology*.[15] Ten years later the 6th case of the erythrodermic form of sarcoidosis with systemic involvement

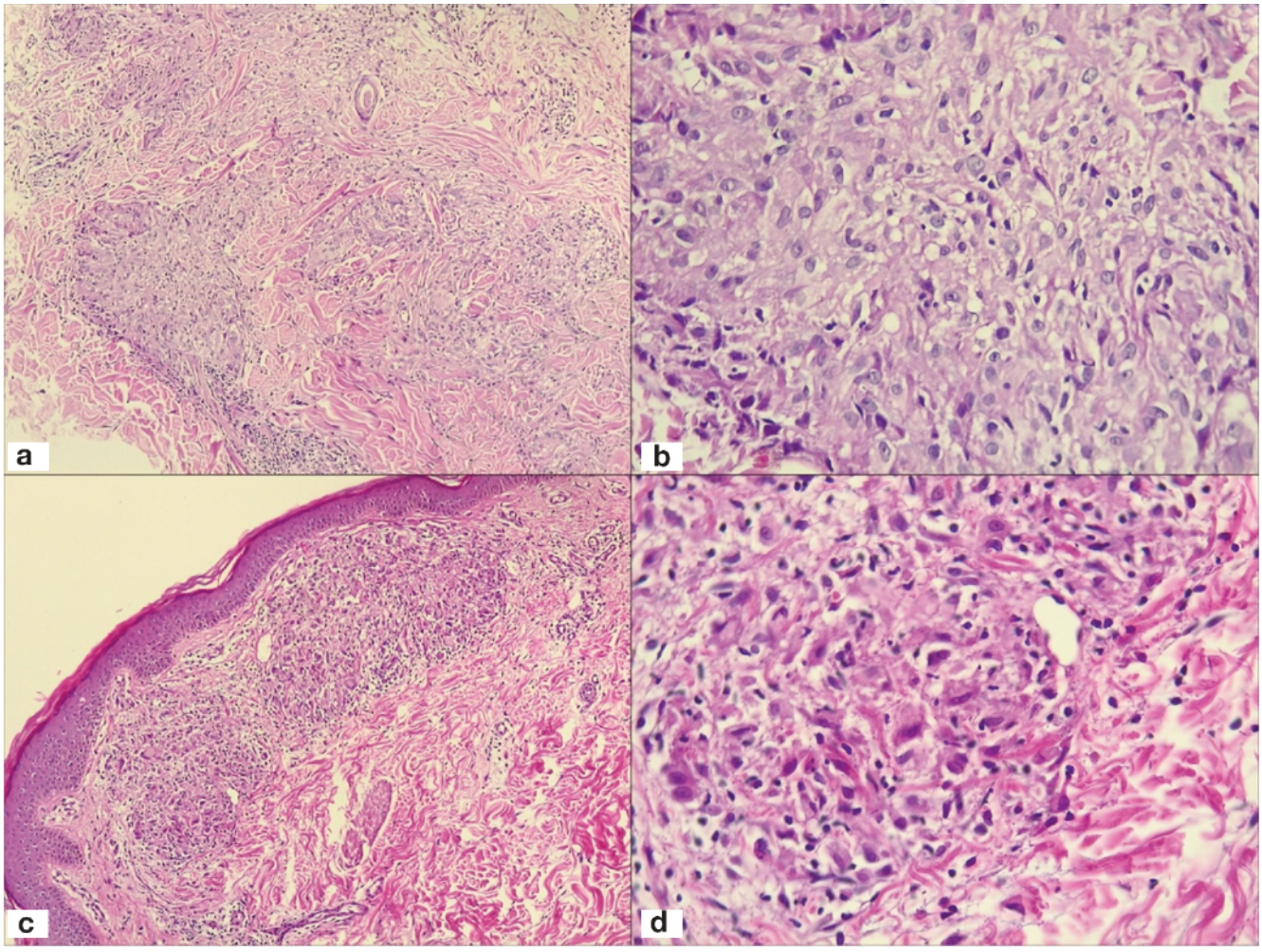

Figure 3. Cutaneous sarcoidosis: orthohyperkeratosis horizontally alternating with parakeratosis, uniform acanthosis with elongation and confluence of the distal parts of the epidermal ridges, diffuse sarcoid granuloma band of epithelioid cells and lymphocytes with single Langhans-type giant cells in the upper and middle dermal segments. a) 1450×100 [hematoxylin and eosin stain (H&E)] - sarcoid granulomas composed of well-differentiated syncytium of epithelioid cells, delimited by a lymphoid shaft, located in the middle dermal segment; b) 1450×400 (H&E) - epithelioid cells with centrally located oval nuclei with evenly distributed chromatin and large bright cytoplasms; c) 1451×100 (H&E) - well-differentiated sarcoid granulomas located in the papillary dermis; d) 1451×400 (H&E) - sarcoid granuloma represented by epithelioid cells with centrally located nuclei and light cytoplasm.

was reported.[16] The 7th official case of the erythrodermic form of sarcoidosis was published only in 1990 by Italian dermatologists from Florence.[17]

The interpretation of the data concerning the occurrence of a sarcoid-type reaction within the Sézary syndrome,[18] fitting again into the framework of cross-mediated autoimmunity when the tissue homeostasis integrity (molecular/antigenic mimicry) is disturbed, remains questionable due to the new antigens in the body (such as tumor cells, for example).[1-3]

The 9th case of the erythrodermic form of sarcoidosis was also described as a rare form of sarcoidosis in Asia in 2003.[19] Erythrodermic sarcoidosis was also described within 14 months of etanercept therapy in a patient with rheumatoid arthritis and was later classified as a possible side effect of the biologic therapy.[20]

According to the clinical data, the involvement of the skin, within the framework of sarcoidosis in the above-described patient, is around 90-92% (Figures 1 and 2).

By definition, erythrodermia in a given disease requires skin involvement of at least 90% or more, so we can conclude that this case is meeting the criteria for erythrodermic sarcoidosis/erythrodermic sarcoid.

After a careful analysis of the literature data, we believe that we describe the 11th case of the erythrodermic form of sarcoidosis registered in scientific databases worldwide.

In fact, this is also the first case of the erythrodermic form of sarcoidosis as a side effect occurring within the framework of vaccination with VAXZEVRIA/ChadOx1-S for COVID-19.

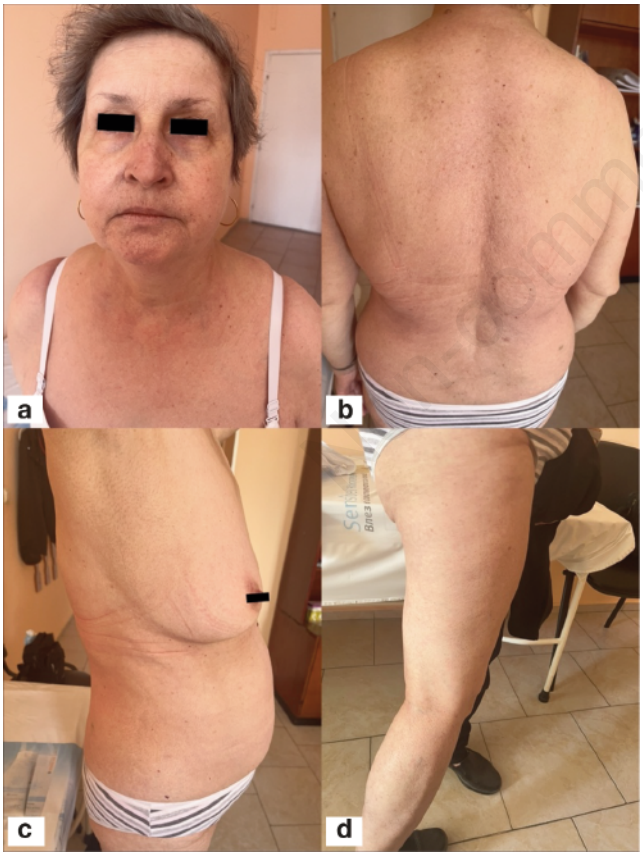

Figure 4. a-d) Patient's outcome after successful treatment for sarcoidosis. No signs of suberythrodermia.

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