CASE REPORT

Post-partum recurrent sarcoidosis associated with type 1 diabetes mellitus

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SUMMARY

Immunologic abnormalities observed in sarcoidosis may suggest a link between this affection and autoimmune endocrine diseases. Indeed a high frequency of autoimmune thyroid diseases is observed in sarcoidosis. However association of type 1 insulin-dependent diabetes mellitus with sarcoidosis is rare. We report the case of a type 1 diabetic woman in whom clinical and biological signs of sarcoidosis appeared after her first pregnancy with a relapse in the post-partum period of a second pregnancy. Diagnosis of sarcoidosis was established on characteristic cutaneous, articular and pulmonary manifestations associated with elevated plasma levels of angiotensin converting enzyme. From this case, association between type 1 diabetes mellitus and sarcoidosis has been discussed as well as reciprocal relationship between sarcoidosis and pregnancy. Since familial history of sarcoidosis was present in this case, familial aspects of sarcoidosis have also been reviewed.

Key-words: Type 1 Diabetes Mellitus · Sarcoidosis · Pregnancy.


RéSUMÉ

Sarcoidose récidivante du post-partum et diabète de type 1

Du fait des anomalies immunologiques observées au cours de cette maladie, la sarcoidose pourrait être rapprochée des endocrinopathies auto-immunes. Mais, si une fréquence élevée de pathologie thyroïdienne auto-immune est rapportée au cours de la sarcoidose, l’association diabète de type 1 et sarcoidose est rare. Nous rapportons le cas d’une patiente diabétique de type 1 qui a présenté une sarcoidose diffuse dont les premiers signes sont apparus dans les suites de sa première grossesse et qui a présenté une récidive dans le post-partum d’une seconde grossesse. Le diagnostic a été établi sur la base d’atteintes cutanées, articulaires et pulmonaires caractéristiques et sur l’élévation de l’enzyme de conversion de l’angiotensine. A propos de ce cas, l’association diabète de type 1 et sarcoidose est discutée de même que l’influence réciproque de la sarcoidose et de la grossesse. La patiente ayant des antécédents familiaux de sarcoidose, le caractère familial possible de la maladie est également envisagé.

Mots-clés : Diabète de type 1 · Sarcoidose · Grossesse.

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Sarcoidosis is a systemic disease occurring in patients with a genetic predisposition after an exposure to yet unknown transmissible environment agents. The histological hallmark is a non-caseating granuloma. Its clinical presentation is protean and its evolution highly unpredictable. All the organs can be involved and there are multiple clinical manifestations [1]. Initial symptoms most often involve the lungs with bilateral hilar lymph nodes and pulmonary infiltrate, the skin (macules, papules, subcutaneous nodules, erythema nodosum) and the eyes (anterior uveitis and conjunctival impairment with small yellow nodules) [2]. Spontaneous recovery occurs in some patients whereas others worsen or relapse even after an apparent recovery.

The cause of sarcoidosis remains obscure and several factors could play a role: environment, infection, genetic and immunologic factors [1]. In sarcoidosis, T lymphocytes in affected organs are of the so-called T helper 1 phenotype, producing interferon-γ and interleukin-2. It seems to be a generic response to a variety of antigens and it has been observed in other granulomatous disorders. In time, CD4 and CD8 lymphocytes, and to a lesser extent B lymphocytes, form a rim around the granuloma. Definitely, sarcoidosis is not an autoimmune disease but it coexists with several autoimmune disorders [1]. In sarcoidosis there is a polyclonal activation of B lymphocytes (delayed hypersensitivity, secondary autoimmune) in reaction to one or several exogenous antigens. In autoimmune diseases, there is an immune response induced by non-recognition of “self” antigens like thyroperoxidase, thyroglobulin or TSH receptor in thyroid autoimmune disease or islet cells components, GAD or IA2 in type 1 diabetes. Endocrine disorders are a well-known target for autoimmune and some associations between sarcoidosis and autoimmune endocrine disease have been published [3, 4] as well as autoimmune non endocrine disease [5]. However, type 1 diabetes associated to sarcoidosis seems very uncommon. Pregnancy is a circumstance when immune mechanisms are involved. During pregnancy, immune tolerance decreases antibodies and autoantibodies production but autoimmunity is exacerbated shortly after delivery. We can figure out that pregnancy is able to induce a first occurrence of sarcoidosis or a recurrence during post partum.

We report here the case of a type 1 diabetic woman with clinical manifestations of sarcoidosis in post partum that were observed during two successive pregnancies.

Case report

A 29 year-old woman with type 1 diabetes discovered when she was 9 took advice in 1994 because she wanted to conceive. Her diabetes was complicated by a laser-treated retinopathy and a retinal tearing treated with cryotherapy. In her personal history, no other element was noticed. In her familial history, sarcoidosis in the skin had occurred in her mother and pulmonary sarcoidosis in her brother. After insulin therapy intensification, haemoglobin A1c was 6.6% and she was able to conceive in December. Her pregnancy was uneventful and she delivered a healthy boy in August 1995. During the post partum, she complained about dyspnoea and cough and an inflammatory process involving ankles, knees, wrists and fingers. This arthritis was associated with subcutaneous nodules, papules and erythema observed on her legs and thighs (Fig 1) and on her face. Huge hilar and mediastinal lymph nodes were present on her Chest X-ray with diffuse bilateral nodular opacities (Fig 2). Serum angiotensin-converting-enzyme levels were 141 IU/l (N < 61). A diagnosis of systemic sarcoidosis was made and a treatment with non steroidal anti-inflammatory drugs, topical corticosteroids followed by hydroxychloroquine led to a complete recovery within one year.

In 1999, a second pregnancy was wished. Insulin was given with a pump and a pregnancy, begun in April, was uneventful until delivery in December. At this time, a caesarean was performed due to toxemia and a breech presentation. A 4,300g boy in good health was born. In April 2000, new sarcoidosis systemic symptoms were noted, similar to the first episode: skin lesions, polyarthralgia, mediastinal...
lymph nodes and ocular manifestations (anterior and intermediary uveitis with a decrease in visual acuity). With non steroidal anti-inflammatory treatment and topical corticoids, the disease remitted again within a few months. Diabetes was correctly treated (HbA1c 7.3%) and this woman did not relapse until now.

**Discussion**

In this diabetic patient, sarcoidosis was diagnosed after her first delivery and relapsed after her second pregnancy. This case allowed us to discuss the relationships between sarcoidosis and pregnancy on one hand and the role played by autoimmunity (type 1 diabetes).

Sarcoidosis is a disease observed in both sexes between age 30 to 40, a time when women are in a reproductive period. Therefore, it is obvious that relations between pregnancy and sarcoidosis can be observed. Several publications claim that sarcoidosis has no influence upon pregnancy and delivery, both being usually normal. For instance, Ellafi et Valeyre [6] mentioned no increased risk for malformations, miscarriages or premature deliveries in usual cases. The single exception would be a very active disease treated with corticosteroids leading to an increased risk of premature delivery. Similar results were observed by Abric et al. [7]: among 11 childbearing women with very active sarcoidosis treated with corticosteroids followed during their pregnancy, only 3 cases of hypotrophic children have been found. Their conclusion is the same: besides a possible (but not systematic) increased risk of child hypotrophy there is no deterministic effect of sarcoidosis during pregnancy. Concerning neonates, there are no studies about long term development of children born from mothers with sarcoidosis but there is no known congenital form of sarcoidosis. Ellafi et Valeyre [6] stated that there is no answer to the question about transmission from the mother to the child. In any case, this risk seems to be tenuous. We would like to stress that the children born from our patient are in good health and did not present symptoms evoking sarcoidosis until now.

On the other side, pregnancy does not seem to modify the evolution of sarcoidosis. No increasing relapses occur during pregnancy when the disease is mild and inactive [6]. In Abric’s report, no relapse during pregnancy was observed in cured sarcoidosis; inactive forms of sarcoidosis remained so and active forms’ evolution was various: some lessened and some worsened. The major risk of relapse is described in post partum, between 3 to 6 months after delivery in most cases [6] and sometimes one year after delivery [7]. Our clinical case is similar to already reported evolutions: the first attack occurred three months after delivery and the relapse happened 4 months after childbirth. There was no symptom or sign of sarcoidosis during both pregnancies. This kind of evolution observed in sarcoidosis (new symptoms after childbirth) is exactly what is observed in case of autoimmune pathologies, mostly in autoimmune endocrine disease.

A high frequency of autoimmune endocrine disorders (until 20%) has been quoted in patients with sarcoidosis [4]. Therefore, a frequent association between sarcoidosis and type 1 diabetes should be observed since this autoimmune endocrine disease is one of the most frequent. In contrast, the association sarcoidosis and type 1 diabetes is rare and the autoimmune endocrine disorders associated with sarcoidosis interests mainly thyroid pathology. Four cases with the association of sarcoidosis and type 1 diabetes have only been published and it has always concerned sporadic cases. In one case, type 1 diabetes happened in a patient with polyglandular autoimmune disease type III [3]. In two cases, the association was sarcoidosis, ulcerative colitis and type1 diabetes [8, 9]. In the fourth case, sarcoidosis preceded type 1 diabetes [4]. This case appears to be the fifth published case but moreover seems the first one in which sarcoidosis was diagnosed in a type 1 diabetic woman in post partum of a first pregnancy with a relapse after a second childbirth.

In our case, sarcoidosis was found in the history of patient’s family. Her brother and her mother had each been treated for sarcoidosis and this underline the familial component of the disease [9, 10]. According to a recent study, parents and siblings in black American patients with sarcoidosis have a 2.5 to 3 times higher risk to present signs of sarcoidosis compared to general black population [11]. This observation strengthens a role for genetic factors in the pathogenesis of the disease. The occurrence of two attacks of sarcoidosis in our patient with familial history of sarcoidosis could be fortuitous because sarcoidosis in post partum has been described in non diabetic women.

**Conclusion**

Sarcoidosis is a protean disease and its pathology is still unclear. Several immune abnormalities and its evolution...
during pregnancy could suggest a link to autoimmune disease since it has been described associated with many autoimmune endocrine disease. However, sarcoidosis is not an autoimmune disease because a polyclonal activation of B lymphocytes in reaction to one or several exogenous antigens is observed. In autoimmune endocrine disease, B lymphocyte reaction is directed against a few unknown or known antigens: for instance thyroperoxidase in autoimmune thyroiditis, anti-islet cells antigens or glutamic acid decarboxylase (GAD) in type 1 diabetes. The association of sarcoidosis and type 1 diabetes is infrequent and our clinical case seems to be the first published case occurring during post partum in a type 1 diabetic female with a recurrence after a second pregnancy. The occurrence of skin lesions, joint pain or pulmonary symptoms during post partum in a type 1 diabetic patient should make consider sarcoidosis as a possible diagnosis, although the association is rare.

References


Sarcoidosis and type 1 diabetes

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