Sarcoidosis with Takayasu arteritis: a model of overlapping granulomatosis. A report of seven cases and literature review

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Abstract

Objective: To describe the features of exceptional coexisting Takayasu arteritis (TA) and sarcoidosis, two conditions of unknown cause associated with a common immunologic pattern.

Methods: We report seven cases of concomitant sarcoidosis-Takayasu or Takayasu-like vasculitis, observed in two referral centers between 1995 and 2015.

Results: All patients were female. The mean age at sarcoidosis diagnosis and TA diagnosis was 36 and 37 years, respectively. Sarcoidosis occurred in 86% of cases before or together with TA. Sarcoidosis always had a classic expression except for one renal localization. Sarcoidosis was not severe and mostly non-treated (86%). In all cases of TA, supra-aortic arteries were involved; in only two TA cases a more diffuse inflammatory arterial involvement was noted. In one case, Takayasu arteritis occurred despite immunosuppressive therapy given for sarcoidosis. All patients received for TA a treatment with corticosteroids associated with methotrexate (four cases), infliximab (one case) or tocilizumab (one case). After a mean follow-up of 89 months, TA always improved and no death was observed.

Conclusions: TA stands as pathology associated with sarcoidosis. TA occurred in three cases among 50. When sarcoidosis preceded TA, a recovery of sarcoidosis was achieved mostly without treatment. TA is a prognostic and therapeutic factor. Immunosuppressive treatment, including steroids, led to a good prognosis for TA as well as for sarcoidosis.

Key words: sarcoidosis, Takayasu arteritis.

INTRODUCTION

Takayasu arteritis (TA) is a chronic large vessel vasculitis of unknown origin, affecting mainly the aorta, its branches and pulmonary arteries. Histologic pattern is characterized by granuloma mainly in the media and/or adventitia of the involved vessels associated with intima fibrous thickening and the disruption of elastic laminae. Pro-inflammatory cytokines play a pathogenic role. TA affects predominantly young female adults. Clinical findings, biological data and imaging must correspond to Takayasu diagnosis criteria as established in 1990 by the American College of Rheumatology.[1] The disease is characterized by vascular symptoms associated with constitutional signs, high blood pressure (especially in cases of reno-vascular involvement) and arthralgia. The chronic phase of TA is characterized by

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symptoms related to vessels stenosis or occlusion. Diagnosis can be made, combined with clinical features and biological inflammatory markers, by ultrasound color Doppler (USCD), computed tomography (CT) scan, arterial magnetic resonance imaging (MRI) or formal arteriography. Uptake of ^{18}F fluorodeoxyglucose (^{18}FDG) on positron emission tomography (PET)-CT as well provides important information on disease activity.

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology. The most common organs affected are lymph nodes, lungs, skin and eyes. Granulomas consist of a central zone with epithelioid cells, macrophages, multinucleated giant cells and active CD4 lymphocytes. The peripheral zone constitutes macrophages, fibroblasts, and CD4 and CD8 lymphocytes. Sarcoidosis diagnosis must meet with international criteria including clinical, biological, radiological, histological evidence associated with the exclusion of others factors which can induce a granulomatous reaction.[2]

Reported cases of vasculitis in patients presenting with sarcoidosis are exceptional. Few cases of sarcoidosis together with granulomatous vasculitis such as Takayasu or Takayasu-like large vessel vasculitis have been described.[3–18] Interestingly, in both diseases pro-inflammatory cytokines and among these, tumor necrosis factor alpha are increased and play a pathogenic role in the development of the disease.

MATERIEL AND METHODS

We report seven cases of concomitant sarcoidosis and Takayasu vasculitis, observed in two referral centers of internal medicine between 1995 and 2015. Five cases represent 0.7% of the 693 sarcoidosis cases observed since 1995 and 4% of the entire cohort of Takayasu. For all seven cases, sarcoidosis diagnosis fulfilled the international criteria except one case with no proven biopsy. Sarcoidosis was documented by clinical signs, chest radiography and respiratory tests, biological abnormalities (routine test and angiotensin enzyme convertase dosage), and histological pattern (bronchial, exocrine gland or renal biopsies). Sarcoidosis disease activity was assessed by clinical signs, radiography, respiratory tests and biological tests.

Takayasu diagnosis fulfilled the 1990 American College of Rheumatology criteria. For all patients, Takayasu disease was documented by clinical signs (symptoms and /or by clinical signs, vascular bruit, marked difference in blood pressure between limbs), biological abnormalities (routine test) and imaging techniques including echography, CT angiography, MRI, PET-CT or formal arteriography. Disease activity in TA was assessed with National Institutes of Health criteria.

RESULTS

Main features, treatment and course of the seven patients with concomitant sarcoidosis and TA are summarized in Table 1. All patients were female, three patients were Caucasian, three originated from North Africa and one was Black. The mean age at sarcoidosis diagnosis and TA diagnosis was 36 and 37 years, respectively. The diagnosis of sarcoidosis was performed in 86% of cases before ($n = 4$) or simultaneously ($n = 2$) to TA. Out of the four patients diagnosed with sarcoidosis before TA, none presented either arterial clinical signs or any major inflammatory syndrome at sarcoidosis diagnosis as opposed to what has been observed during the acute phase of TA. Except in case two, sarcoidosis expression was classic with mediastinal lymphadenopathy and/or pulmonary localization (six cases), erythema nodosum (four cases), joint (four cases) and ocular (two cases) involvement. Tuberculin test was negative in 4/7 cases. Two patients had

Table 1 Characteristics of sarcoidosis (S)

	Age at diagnosis of S	Ethnicity	Sex	S features	Treatment of S	Course of S
Case 1	19	North Africa	F	Stage II	none	Recovery
Case 2	53	North Africa	F	Uveitis, renal insufficiency	Prednisone, MTX	Recovery
Case 3	50	North Africa	F	Stage I, erythema nodosum, arthralgia	None	Recovery
Case 4	26	Caucasian	F	Stage II, nasal signs, exocrine glands	None	Recovery
Case 5	53	Black	F	Stage I, erythema nodosum, arthralgia, uveitis	None	Recovery
Case 6	25	Caucasian	F	Stage I, erythema nodosum, arthralgia	None	Recovery
Case 7	29	Caucasian	F	Stage I, erythema nodosum, arthralgia	None	Recovery

Table 2 Characteristics of Takayasu arteritis (TA)

	Age at TA diagnosis	Chronology	TA features	Abnormal CRP	Vessel lesions in TA USCD/CT scan	Treatment of TA	Course Follow up (months)	Last treatment
Case 1	19	Concomitant	EN, arthralgia	+	Stenosis of proximal then complete obstruction of left axillary artery. Diffuse narrowing of right artery	Prednisone, aspirin	Remission 36 months	Prednisone: 5 mg/day
Case 2	54	1 year after S S in remission	Limbs claudication, HTA, vascular bruit	+	Stenosis of common and left external iliac artery; occlusion of external right iliac artery; narrowing of left renal and subclavian arteries	Prednisone, MTX, aspirin	Remission 38 months	Prednisone: 5 mg/day MTX: 15 mg/week
Case 3	53	3 years after S S in remission	Visuals signs	+	Diffuse narrowing of aortic bifurcation and left subclavian arteries	Prednisone, aspirin	Remission 60 months	Prednisone: 5 mg/day
Case 4	27	1 year after S S still active	Vascular bruit, HTA	+	Stenosis of left subclavian, axillary and humeral arteries	Prednisone, MTX	Remission 132 months	Prednisone: 5 mg/day
Case 5	52	1 year before S	Limbs claudication, TA active	+	Stenosis of left renal artery, coeliac artery, superior and inferior mesenteric arteries and right subclavian artery	Prednisone, MTX, IFX, TOCI	Remission 180 months	Prednisone: 10 mg/day, MTX: 15 mg/week
Case 6	25	Concomitant	Limbs claudication	+	Stenosis of axillar arteries	Prednisone	Remission 120 months	None
Case 7	30	1 year after S S in remission	Limbs claudication	+	Stenosis of left axillar, carotid stenosis, occlusion of vertebral artery	Prednisone, MTX, IFX	Remission 60 months	None

TA, Takayasu arteritis; CRP, C-reactive protein; EN, erythema nodosum; HTA, high blood pressure; USCD/CT, ultrasound color Doppler / computed tomography; MTX, methotrexate;IFX, infliximab; TOCI, tocilizumab

phlyctenular reaction. Histopathologic features for sarcoidosis were obtained in all cases but one. For the latter, sarcoidosis diagnosis was determined as the patient presented with Lofgren syndrome associated with characteristic anterior uveitis and lymphocytic alveolitis. Except in case 2 (renal localization imposed immunosuppressive therapy), all patients with sarcoidosis did not need treatment. In all cases, sarcoidosis improved and was considered in remission at the end of the follow up when patients presented with a regression of thoracic disease with no clinical and biological abnormalities.

The onset of TA occurred in most non-treated patients. Case 2 was receiving prednisone (5 mg/day) and methotrexate (MTX, 15 mg/week) when arterial symptoms appeared, and case 6 was receiving 7 mg/day of prednisone. In cases 1 and 6, arthralgia and arteritis claudication led to discovery of asymptomatic thoracic sarcoidosis. Serological and microbiological studies ruled out infectious diseases. Diagnosis of TA was confirmed by characteristic abnormal results of echography (7/7), pan-aortic CT scan (1/1), MRI (3/3) and arteriography (3/3). In one case, MRI enhancement and ^{18}FDG-PET scan uptake was correlated to define disease activity. In three cases (cases 2, 3 and 5), TA was associated with diffuse vasculitis (Table 2). For TA, all patients received corticosteroids associated with MTX (four cases) and anti-platelet treatment (three cases). Two patients with phlyctenular tuberculin test received an anti-tuberculosis treatment (cases 2 and 5). Two patients received infliximab (5 mg/kg), MTX (0.3 mg/kg/week) and prednisone (between 0.5 and 1 mg/kg/

Table 3 Sarcoidosis (S) and Takayasu arteritis (TA), literature review

Author (ref)	Sex / age	Chronology of S/TA	Localization	Treatment	Course
Weiler *et al.*[3]	F/39	S then TA ≠ 12 years	Aortic insufficiency	Surgery, glucocorticoid	Remission
Hamzaoui *et al.*[4]	F/34	Concomitant	Left subclavian stenosis	Glucocorticoid + methotrexate	Remission
Korkmaz *et al.*[5]	F/29	S then TA ≠ 4 years	Occlusion of left subclavian, vertebral arteries and mesenteric arteries; diffuse narrowing left common carotid artery	Glucocorticoid + azathioprine	Remission
Schapiro *et al.*[6]	F/42	S then TA ≠ 2 years	Diffuse narrowing of aortic bifurcation and subclavian arteries	Glucocorticoid + cyclophosphamide	Remission
Taeib *et al.*[7]	F/11	S then TA ≠ 2 years	Stenosis of aortic arch	–	Remission
Robaday *et al.*[8]	F/26	S then TA ≠ 1 year	Narrowing of humeral, axillary and subclavian arteries	Glucocorticoid	Remission
Rafiq *et al.*[9]	F/28	TA then S ≠ 13 years	Aortic calcifications and proximal iliac stenosis	–	Remission
Izumukawa *et al.*[10]	M/12	TA then S ≠ 12 years	Narrowing thoracic and abdominal aortic; left subclavian and renal stenosis	Glucocorticoid	Remission
Vaurs *et al.*[11]	M/20	S then TA ≠ 10 years	Subclavian artery	Glucocorticoid + methotrexate	Remission
Ishii *et al.*[12]	M/72	Concomitant	Right pulmonary artery	–	Death due to diffuse sarcoidosis
Kerr *et al.*[13]	F/32	Concomitant	Subclavian steal syndrome	–	Remission
Ri *et al.*[14]	F/67	Concomitant	Occlusion of superficial artery, occlusion of subclavian artery and stenosis of right coronary artery	Surgery	?

day). One patient received tocilizumab every month after failure of infliximab. The remission was confirmed with the disappearance of biological inflammatory processes and imaging activity. After a mean follow-up of 89 months (36 to 180), all patients were considered in remission for sarcoidosis and TA.

DISCUSSION

These seven cases herewith represent to our knowledge the largest series of concomitant presentation of sarcoidosis together with TA. Main conclusions drawn from this series are: (i) when sarcoidosis preceded TA, a recovery of sarcoidosis was achieved mostly without treatment; (ii) TA occurred in three cases over 50 years; and (iii) immunosuppressive treatment, including steroids, led to a good prognosis.

Aortitis may occur in many conditions, including syphilis, fungal infections and tuberculosis. These hypotheses were ruled out by microbiological studies. Takayasu arteritis has been described in association with various auto-immune disorders[18] such as Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis and ankylosing spondylitis. Sarcoidosis is very rarely reported as associated with vasculitis, such as giant cell arteritis or granulomatosis with polyangiitis.[17] Less than 15 cases of TA plus sarcoidosis have been described in the literature (Table 3),[3–14] mostly observed in women (77%) as in our series. We noted that sarcoidosis generally precedes TA as in the series by Weiler *et al.*[3] However, in the latter the time lag between the two diseases was often 8 or more years (80% of cases) compared to the longest interval of 3 years in our series. In few reported cases[12,13] and one case in our series (case 5), TA preceded sarcoidosis. As in the Weiler *et al.* study,[3] the aorta and/or its major branches were affected, with a constant inflammatory process of supra-aortic arteries. We found three cases of diffuse vasculitis, always noted only in the oldest patients (>50 years old). In our series, several points differ from Weiler *et al.*'s conclusions.[3] (i) The proportion of uveitis is less frequent (29% *vs*. 50%); (ii) TA or Takayasu-like syndrome appeared in three cases after 50 years. (iii) Glucocorticoids alone were not sufficient in 57% of cases. MTX and/or biotherapy was necessary for four patients. Other than the treated renal sarcoidosis case, all our sarcoidosis cases had spontaneous resolution, as observed in the literature for stage I or II sarcoidosis in 60% of cases. At the end of the course, all our patients recovered from sarcoidosis and TA.

These cases prompt discussion about these two diseases. TA and sarcoidosis may be related as they are characterized by certain nonspecific immuno-inflammatory abnormalities. The fact that sarcoidosis preceded the vasculitis manifestations in almost all cases suggests that TA or TA-like granulomatous vasculitis could be a complication/manifestation of sarcoidosis. Nevertheless, one can maintain that TA stands as pathology-associated with sarcoidosis. The arguments supporting the latter are the presence of TA before sarcoidosis, and the association of TA with other granulomatous vasculitis with a common and intricate etiopathogenic mechanism.[8]

CONCLUSION

We herein described seven cases of TA or TA-like granulomatous vasculitis associated with sarcoidosis. TA occurred in three patients above 50 years. When sarcoidosis preceded TA, a recovery of sarcoidosis was achieved without treatment. Arteritis was the prognostic and therapeutic factor. Immunosuppressive treatment, including steroids, led to a good prognosis for TA as well as for sarcoidosis. During the course of sarcoidosis, a granulomatous arteritis may occur. Distinction between large vessel vasculitis associated with sarcoidosis and sarcoidosis with TA may be difficult to differentiate. The final diagnosis label of sarcoidosis with TA is based upon indisputable evidence of TA criteria. Physicians should be aware of this possibility. Complete vascular clinical examination should be performed to detect inflammatory arteritis, especially in cured sarcoidosis presenting a relapse of the biological inflammatory process.

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