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Review

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Cardiac Inflammatory Pseudotumors in Behçet's Disease

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Abstract

Introduction: Cardiac non-specific inflammatory pseudotumors (NSIPT) are exceptionally associated to Behçet's disease (BD) and represent a real diagnostic and therapeutic challenge. The meaning and the mechanisms of this association are not yet well understood. The purpose of this paper is to study the epidemiologic, therapeutic, and evolutionary characteristics of cardiac NSIPT during BD

Methods: Systemic review of all reported cases of cardiac NSIPT associated with BD.

Results: We found only 6 cases of NSIPT associated with BD. Of these six patients, 4 were men (66.66%) and 2 were women (33.33%): Sex ratio =2. The average age was 26.66 years (9-35 years). The pseudotumor was unique in all cases. The chronology of occurrence of these NSIPT compared to the underlying angiitis was variable: inaugural of the disease in 4 cases, and complicating a previously known BD in 2 cases. The surgery was performed in all cases. It was carried out for diagnostic purpose in 4 cases, and therapeutic in the other 2. Additional medical treatment based on systemic corticosteroids with or without immunosuppressants was indicated in 4 patients. The evolution was favorable in 5 cases and a single case was quickly fatal. Recurrence of NSIPT was reported in one patient (20%).

Conclusion: The results of this review suggest a very likely association between BD and cardiac NSIPT; especially because of the scarcity of these two conditions in the general population, and the epidemiological characteristics clearly different from those of cardiac NSIPTs in the general population. The pathogenic mechanisms common to these two conditions (immune, inflammatory, reactive, and vascular) reinforce this causal link. The main differential diagnoses of these pseudotumors during BD remain cancer and intracardiac thrombosis.

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Introduction

Behçet's disease (BD) is a systemic vasculitis affecting all vessels (arteries and veins) of any size (small, medium, and large) [1]. It has a predilection for the young male subject, and is particularly common in countries around the Mediterranean, the Middle East, and Asia [2-4].

Non-specific inflammatory pseudotumors (NSIPTs) represent a group of heterogeneous conditions of unknown etiology [5] which can affect all organs, and often represent a real diagnostic and therapeutic challenge [5,6].

NSIPTs are only exceptionally described in association with BD; indeed, and since the first histologically documented observation that was published in 1996 reporting a NSIPT of the terminal ileum during BD [6], only a few other localizations have been reported sporadically: heart [7], brain [8,9], orbit [10,11], kidney [12], and colon [13]. The meaning and the mechanisms of this association are not yet well understood.

The purpose of this paper is to study the epidemiologic, therapeutic, and evolutionary characteristics of cardiac NSIPT during BD.

Methods

Systematic review of the literature with a wide and careful bibliographic search that targets published cases associating cardiac NSIPT with BD from 1937 until the 1st of April 2019.

This search was carried out in the following databases and search engines: Pubmed/Medline, Sciencedirect, Embase, Google Scholar, Scopus and Hinari in French and English languages; using the following keywords: Adamantiades-Behçet disease, Behçet's disease, Behçet's syndrome, crossed with the keywords: Cardiac pseudotumor, Inflammatory pseudotumor, Nonspecific inflammatory pseudotumor, and heart.

Only cases of cardiac NSIPT confirmed by histological examination were selected for this review. Cases initially diagnosed as cardiac NSIPT, but whose subsequent histopathological examination resulted in intracardiac thrombosis, were excluded.

Results

The review of the literature revealed six cases of cardiac NSIPT during Behçet's disease and confirmed by post-operative histological examination [14-18].

Of these six patients, four were men (66.66%) [14,16-18], and two were women (33.33%) [15,18]. The sex ratio was thus 2. The average age was 26.66 and the age extremes were 9 [18] and 35 years [18]. Five patients were adults and only one was 9 years old.

The pseudotumor was unique in all cases. The chronology of occurrence of these NSIPT compared to BD was variable: the NSIPT was inaugural of the disease in four cases [16-18], and complicating a previously known BD in two cases [14,15].

The surgery was performed in all cases [14-18]. It was carried out for diagnostic purpose in four cases (inaugural forms of the disease) [16-18], and therapeutic in the other two cases (severe cases of right heart failure) [14,15]. Additional medical treatment based on systemic corticosteroids with or without immunosuppressants was indicated in four patients [16-18]. The evolution was favorable in five cases. A single case was quickly fatal postoperatively, before initiating a medical treatment [14].

Recurrence of NSIPT was reported in one patient (20%): early postoperative recurrence (after 15 days of intervention) due to the lack of associated medical treatment, but subsequent progression after systemic corticosteroid therapy was favorable [18].

Table 1 summarizes the different epidemiological, therapeutic and evolutionary characteristics of these cases.

Discussion

This review has demonstrated, despite the few limitations, an association that does not seem to be a mere coincidence between BD and cardiac NSIPT. The main limitations are the non-inclusion of cases of NSIPT associated with BD that could have been published in local or national journals not indexed in the major indexing systems or not listed in the consulted databases, as well as the very small number of cases found.

Table 1. Cardiac NSIPT associated with BD: Cases found in the world literature.

Authors /Ref	*Age/sex*	*Localization*	*Treatment*	*Number*
Leitão B. 2009 [14]	22/M	IVS	Surgery (death)	1
Yao FJ.2012 [15]	35/F	Free wall of the RV	Surgery	1
Zou Y. 2012 [16]	26/M	Free wall of the RV	Surgery + medical treatment	1
Unal Aksu H. 2014 [17]	33/M	Free wall of the RV	Surgery + medical treatment	1
Leibowitz D. 2014 [18]	35/M 09/F	Free wall of the RV Free wall of the RV	Surgery + medical treatment Surgery + medical treatment	1 1
Total of cases				06

NSIPT: nonspecific inflammatory pseudotumor, BD: Behçet disease, M: male, F: female, IVS: interventricular septum,

RV: right ventricle.

Association between cardiac NSIPT and BD

NSIPTs have been reported in association with some other systemic vasculitis: granulomatosis with polyangiitis [19,20], eosinophilic granulomatosis with polyangiitis [21], giant cell arteritis [22,23], and Takayasu's disease [24].

The chronic inflammation of the different tissues, the vascular damage, and the immune dysfunction which characterize these affections are the main factors incriminated in the development of these pseudotumors. In addition, there is a potential genetic susceptibility and an indirect involvement of certain used therapies [12,25,26]. All these hypothetical factors of this tumorogenesis-like are validated in patients with BD; this is why some authors think that the association between NSIPT and BD is far from being a mere coincidence [12].

Several findings from our literature review reinforce this hypothesis of a causal link between BD and NSIPT; it is mainly about:

The scarcity of these two conditions: BD is a rare vasculitis with a prevalence which does not exceed 8 to 37/10,000 inhabitants [27,28]. Cardiac NSIPTs are also exceptional [29-31], and since their first description in 1975 by Gonzalez-Crussi F [32], fewer than 30 cases have been reported [31]. Thus, and given the extreme rarity of simultaneously having these two conditions "as a mere coincidence" in the general population, the potentially "promoting" character of the development of cardiac NSIPT presented by this angiitis seems highly probable,

The epidemiological characteristics: the epidemiological characteristics of the cardiac NSIPT associated with BD are clearly different from those conventionally observed for the NSIPT in the general population: in fact, in the general population, the NSIPT are a pathology of the child and the adolescent [26,33-36], while our review of the literature showed a clear predominance of these pseudotumours in the adult with BD. Concerning the sex, in the general population NSIPTs affect both sexes equally [26,33-36], whereas in patients with BD, the distribution of cardiac NSIPT shows a clear male

predominance (sex ratio=2) similar to the distribution of the underlying vasculitis which once again reinforces the causal link,

The localizations of NSIPTs in the heart: the localization of these NSIPT associated with the BD is different from that observed in the general population: in the general population, the auricles represent the classic site of predilection [29,30] whereas the involvement of the right ventricle remains exceptional [30]. These data contrast sharply with cardiac NSIPT's features during BD with right ventricular involvement in the majority of cases (83%) and no atrial involvement.

The significant difference in clinico-epidemiological characteristics between cardiac NSIPT occurring during BD compared to those in the general population, as well as the observed number of cases of NSIPT associated with BD, which appears to be far greater than the number theoretically expected because of the very rare prevalences of the two affections, strongly suggest a direct causal link between BD and the secondary appearance of these NSIPT. Pathogenic mechanisms common to these two conditions reinforce this hypothesis (immunological, inflammatory, vasculitic, reactive, and infectious) [6,25,26].

Differential Diagnosis of Cardiac NSIPT During BD

The main problem posed by this association is a problem of differential diagnosis with cancers occurring during BD, especially since a carcinogenic potential of this vasculitis is currently strongly advanced by several authors [37]; indeed, in large series, cancer occurs in 1.8% to 3.25% of patients with BD [38,39]. These malignant neoplasms have been reported in different organs and tissues in patients with Behçet's disease [37,38,40,41].

This differential diagnosis is often difficult to make because of the absence of specific clinical, biological or radiological signs of the NSIPT.

In addition to primary or secondary cardiac tumors [18]; other differential diagnoses of NSIPT during BD are mainly organized or unorganized intracardiac thrombus [42,43], an infectious endocarditis [16,17] and endomyocardial fibrosis in its pseudo-tumoral form, which is another common complication of BD [44-46].

In cases of cardiac NSIPT occurring during the course of BD, the lack of knowledge of the underlying pathology, particularly in the inaugural forms of the disease, led to excessive and unnecessary surgical procedures, sometimes with rapid recurrence after surgery [15-18]. Thus, some authors advocate that BD, even in the absence of classical clinical signs, be considered as a differential diagnosis of any mass of the right ventricle occurring in the young subject particularly in the Mediterranean and the Middle East [42].

Treatment and Evolution of Cardiac NSIPT Associated with BD

Regardless of the location, treatment of NSIPTs is still controversial and poorly codified; surgical excision is the treatment of choice [26].

In the forms of NSIPT associated with BD, the treatment is mainly based on systemic corticosteroid therapy at high doses, sometimes initiated by intravenous methylprednisolone boli [8], and associated with long-term immunosuppressive drugs. The most commonly used are monthly cyclophosphamide boli and oral azathioprine [9,18].

Biotherapy may be suggested as a second-line treatment for NSIPTs occurring during BD and resistant to conventional first-line treatment, with satisfactory results [47].

Surgery is only available in complicated life-threatening forms [48]; the systemic vasculitis that characterizes this disease often exposes to operative complications and local recurrences [2-4,15]. The majority of surgical procedures found in the literature for these cardiac NSIPTs associated with BD were mainly performed for the inaugural forms of the disease and for fear of a malignant neoplastic process [6,12,16-18].

Thus some authors recommend, especially for the cardiac localizations, to evoke and to look for BD in case of any unexplained heart mass, before considering a surgical excision sometimes heavy and serious [18].

Cardiac NSIPT associated with BD were characterized by a generally favorable prognosis; locoregional recurrence remains rare [15]. Prolonged

follow-up (clinical and radiological) remains however necessary because of the unpredictable evolution of these pseudotumors.

Conclusion

The results of this review suggest a very likely association between BD and cardiac NSIPT; especially because of the scarcity of these two conditions in the general population and the epidemiological characteristics clearly different from those of cardiac NSIPTs in the general population. The pathogenic mechanisms common to these two conditions (immune, inflammatory, reactive, and vascular) reinforce this causal link.

The main differential diagnoses of these pseudotumors during BD remain cancer and intracardiac thrombosis.

This particular cardiac complication of the BD deserves to be known by the clinicians confronted with this vasculitis, in order to diagnose it and initiate the treatment without delay. The specific medical treatment (corticosteroids and immunosuppressants) rapidly introduced is the only guarantee of a good prognosis.

Conflicts of Interest

None

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