

Fever Due to Inflammation in Acute Aortic Dissection: Description and Proposals for Diagnostic and Therapeutic Management

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Few studies have investigated fever secondary to underlying acute aortic dissection. A retrospective analysis of 59 patients was carried out. Diagnostic criteria for fever secondary to underlying aortic dissection were defined. Five patients had a clinical presentation consistent with inflammatory fever due to acute aortic dissection. The main features were: fever occurred within the first 48 hours, the variability in body temperature was significantly less than with infectious fever ($P=.015$), episodes of fever did not affect the patient's general clinical condition, microbiological tests gave negative results, there was no response to empirical antimicrobial treatment, and fever disappeared within 24 hours in those treated with indomethacin. In conclusion, fever due to acute aortic dissection has distinct characteristics that enable it to be distinguished from infectious fever. Good management of this condition should not involve unnecessary diagnostic tests, the inappropriate use of antimicrobials, or a delay in applying the therapeutic measures necessary to treat the underlying aortic dissection.

Key words: *Acute dissection. Aorta. Fever of noninfectious origin.*

Fiebre inflamatoria por disección aguda de aorta: estudio descriptivo y propuesta de abordaje diagnóstico-terapéutico

La fiebre secundaria a la propia disección aguda de aorta ha sido poco estudiada. Se valoró retrospectivamente a 59 sujetos. Se definieron unos criterios diagnósticos de fiebre secundaria a la propia disección. Cinco pacientes presentaron clínica compatible con fiebre inflamatoria por disección aguda. Sus características fueron: fiebre en las primeras 48 horas; variabilidad de temperatura significativamente menor que en la fiebre de etiología infecciosa ($p = 0,015$); no afectación del estado general durante los episodios de fiebre; resultados microbiológicos negativos; ausencia de respuesta a antimicrobianos empíricos; desaparición de la fiebre en 24 horas en los tratados con indometacina. En conclusión, la fiebre por disección aguda de aorta presenta unas características que la hacen distinguible de la fiebre por infección. Un adecuado abordaje de esta patología podría evitar la realización de pruebas diagnósticas innecesarias, el uso inadecuado de antimicrobianos y el retraso de medidas terapéuticas que se pudieran precisar para la propia disección.

Palabras clave: *Disección aguda. Aorta. Fiebre de etiología no infecciosa.*

INTRODUCTION

Acute aortic dissection is associated with a very high mortality rate and usually represents a medical emergency.^{1,2} The association between chronic aortic dissection and fever has been known for years, but very few studies have related fever with

acute aortic dissection. It therefore commonly goes unmentioned as a clinical manifestation of the condition in guidelines. A number of studies have proposed theories regarding the pathophysiology of inflammatory fever in acute aortic dissection.^{3,4} However, none has defined the clinical criteria in such patients that would allow an appropriate early diagnosis to be made. Fever has normally been described in the context of chronic aortic dissection.⁵

METHODS

This retrospective study, which covers a period of 10 years, was performed at the Hospital Universitario 12 de Octubre in Madrid. Patients were recruited

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using the diagnoses recorded in their discharge papers. All aortic lesions visible in imaging tests were deemed to represent an aortic dissection. Fever was deemed present when patient body temperature was $\geq 37.8^{\circ}\text{C}$.

The variables recorded in the present work were sex, age, whether the temperature was taken in the emergency room (yes/no), type of dissection according to the Stanford⁶ classification (A/B), the time elapsed between the beginning of the patient's condition and emergency attention being received, patient temperature in the emergency room, daily minimum and maximum body temperature, and the variation in daily body temperature (calculated by obtaining the mean differences between the daily maximum and minimum). The study did not identify patients with an intramural hematoma or symptomatic aortic ulcer (belonging to the most recent classification of acute aortic syndrome).⁶

All patients with fever were identified and decisions made regarding whether this was due to the dissection; the criteria for inflammatory fever were thus established (defined in Results). Among these patients the following data were noted: analytical abnormalities (leukocytosis $>10\,000/\mu\text{L}$, neutrophilia $>70\%$, lactate dehydrogenase), chest x-ray results, blood, urine, sputum and intravenous catheter culture results, and fever etiology (infectious, medication-induced, post-surgical, inflammatory, or other).

RESULTS

The studied cohort was composed of 59 patients, all with acute aortic dissection (43 [72%] men). The mean age was 60.3 (14.4) years. Forty-seven patients (79%) suffered a type A dissection, and 12 (21%) a type B dissection.

Body temperature had been taken in the emergency room in just 47.46% of patients (28/59), and the following distribution was noted: 22/28 (78.56%) patients were non-febrile, 3/28 (10.72%) had febricula, and 3/28 (10.72%) had fever. All patients had their temperature taken, however, within the first six hours of their hospital arrival. Six died in the first 24 h and 43 underwent surgery (41 with a type A dissection, 2 with a type B dissection).

Five patients of the cohort showed a condition compatible with fever secondary to acute aortic dissection (Table 1). In these patients fever appeared within the first 48 h of the onset of symptoms. The duration of fever in those who did not undergo surgery or in whom diagnosis was delayed, was over 15 days. In these patients the maximum daily temperature was $\geq 37.8^{\circ}\text{C}$ in more than 50% of measurements taken, and $\geq 37^{\circ}\text{C}$ in 90% of measurements. The mean daily variation in the temperature of the 5

patients with inflammatory fever secondary to acute aortic dissection was 0.77 (0.3), 0.73 (0.39), 0.58 (0.28), 0.57 (0.3), and 0.81 (0.25) $^{\circ}\text{C}$. The variation was $<1.2^{\circ}\text{C}$ in 85% of all measurements recorded.

Five patients presented with fever secondary to an infection (Table 1). The mean daily temperature variation in these patients during the febrile episode was 1.5 (0.7), 1.6 (0.6), 2 (0.8), 1.9 (1.1), and 3.1 (1.4) $^{\circ}\text{C}$ respectively. All 5 became afebrile with antibiotic treatment.

The difference in the mean variation of fever between patients with fever secondary to aortic dissection and those with fever of infectious etiology was significant ($P=.015$; 95%CI, 0.33-2.32).

According to the physicians' comments recorded in the examined medical histories, the patients with fever secondary to aortic dissection always showed a 'good general condition.' Chest x-rays showed nothing significant, except in one patient who was seen to have a pleural hemorrhage in the left hemithorax.

The 5 patients in whom fever was retrospectively attributed to their acute aortic dissection had all been subjected to multiple microbiological culture analyses. No results of microbiological interest were returned for four of these patients. The fifth was treated for bacteremia caused by *Staphylococcus aureus* secondary to a catheter infection some time after the fever secondary to the aortic dissection. During the febrile episode attributable to aortic dissection, four patients received different combinations of empiric, wide spectrum antibiotic treatment, despite which their fever remained for more than 2 weeks. In 3 of these 5 patients inflammatory fever secondary to aortic dissection was suspected, and in 2 of these 3 treatment with indomethacin was begun and antibiotic treatment suspended; fever remitted in these patients. Figure shows the abrupt disappearance of fever with the start of indomethacin treatment in 1 patient who had received different antibiotic treatments for 19 days.

DISCUSSION

Papers discussing series of patients with aortic dissection fail to mention fever as an associated manifestation^{7,8}; in fact, even the International Registry of Acute Aortic Dissection⁹ fails to make any mention of this.

This careful, retrospective study of a series of patients with acute aortic dissection allowed the characteristics that discriminate between fever owed to a dissection itself and that owed to an intercurrent infectious process to be identified. The comparison of these groups allowed the identification of 2 patients whose fever was secondary to their acute

TABLE 1. Characteristics of the Patients With Fever Secondary to Acute Aortic Dissection and Those With a Fever of Infectious Origin

Sex/Age	Surgery	Clinical Characteristics of the Fever	Results of Microbiological and Imaging Tests
Patients with fever secondary to acute aortic dissection			
Man/58 years	No	Type B acute aortic dissection from the base of the subclavian artery to the external iliac arteries. Thrombosis proximal to the false lumen. Fever starts on 4th day. Fever prolonged. Good general condition. Inflammatory fever owed to acute aortic dissection	Culture tests negative
Man/31 years	Yes	Marfan syndrome. Aneurismatic dilatation of the descending thoracic aorta from the outflow the left subclavian artery to the iliac bifurcation. Type B acute dissection in the mid third of the ascending aorta with false lumen completely filled by an organized thrombus. Fever initiated at 5 days. Good general condition. Fever remitted with indomethacin. Inflammatory fever secondary to acute aortic dissection	Culture tests negative
Man/63 years	No	Type B acute dissection originating in the distal aortic arch at the outflow of the left subclavian artery, extending to the origin of the iliac arteries. Small thrombus adjacent to the origin of the dissection. Fever started at 48 h. Fever prolonged. Inflammatory fever secondary to acute aortic dissection	Later Staphylococcus aureus infection of a central catheter and nosocomial pneumonia
Woman/63 years	No	Type B acute aortic dissection from the aortic arch until the outflow of the common left iliac artery. Concentric intramural hematoma 11 mm in diameter from the origin of the left subclavian artery to the outflow of the renal arteries. Fever started at 48 h. Prolonged fever. Good general condition. Inflammatory fever secondary to acute aortic dissection	Culture tests negative
Man/52 years	Yes	Type A acute aortic dissection with origin close to the outflow of the brachiocephalic trunk. Aortic arch and descending aorta affected until the origin of the iliac arteries. Fever began 48 h after surgery. Fever prolonged. Good general condition. No response to antimicrobial drugs. Fever remitted with indomethacin. Inflammatory fever secondary to residual aortic dissection following surgery	Culture tests negative
Patients with fever secondary to infectious origin			
Woman/76 years	Yes	Fever secondary to infectious origin	Tracheobronchitis caused by <i>Escherichia coli</i>
Man/61 years	Yes	Fever secondary to infectious origin	Urine infection caused by wide-spectrum beta lactamase-producing <i>E. coli</i>
Man/61 years	Yes	Fever secondary to infectious origin	Bacteremia caused by coagulase negative secondary infection of a vascular catheter.
Man/42 years	No	Fever secondary to infectious origin	Bacteria caused by <i>E. coli</i> of uncertain origin.
Man/69 years	Yes	Fever secondary to infectious origin	Tracheobronchitis caused by methicillin-resistant <i>S. aureus</i>

aortic dissection, but for whom this diagnosis had not been made. Fever secondary to acute aortic dissection was mostly seen in patients with a type B dissection, a situation in which surgery is usually deferred. Fever begins between 48 and 72 h after the dissection occurs and microbiological tests are

negative. The variation in body temperature in this kind of fever is significantly less than that caused by infection, and patients show a 'good general condition' during times when fever is apparent. The last of these clinical data has a very subjective interpretation, but it was repeatedly mentioned

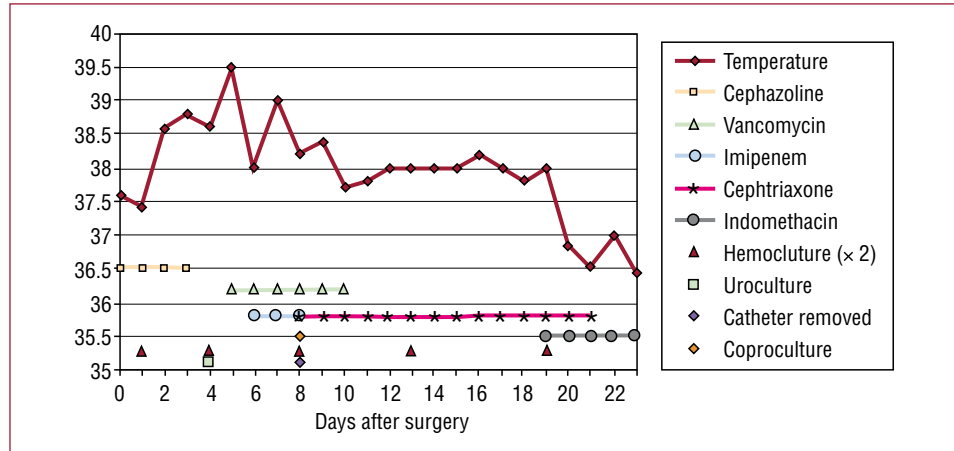


Figure 1. Rapid remission of fever secondary to acute aortic dissection after beginning of indomethacin treatment following 19 days of varied antibiotic treatment.

in the patients' reports. Fever rapidly disappears (in under 24 h) after beginning anti-inflammatory treatment (especially with indomethacin). When the diagnosis is uncertain, it might be reasonable to try a "therapeutic trial" with anti-inflammatory drugs while empirical anti-microbial treatment is maintained.

Only one paper has been published on inflammatory fever in a cohort of patients with acute aortic dissection,⁴ and it was concluded that a significant relationship existed between the size of the thrombus in the false lumen of the dissection and the duration of inflammatory fever. It should be noted, however, that the methods used involved

no objective criteria for defining inflammatory fever secondary to dissection.

Based on the results of the present work, criteria for the diagnosis and treatment of fever secondary to acute aortic dissection are proposed (Table 2).

In conclusion, in subjects with acute aortic dissection there are a number of clinical data that allow one to distinguish between a fever secondary to the dissection itself and a process caused by an intercurrent infection. Their distinction may avoid the undertaking of certain complementary tests, reduce the duration of unnecessary antibiotic treatment, and avoid delay in embarking upon treatment that the patient might need for his/her aortic condition.

TABLE 2. Recommendations for Establishing a Diagnosis of Inflammatory Fever Secondary to Acute Aortic Dissection

1. Determine the temperature of patients with acute aortic dissection upon arrival at the emergency room. The duration of the patient's condition should also be established
2. Determine the variation in temperature over the full 24 h of the day
3. Perform a physical examination every day, along with periodic biochemical, hematological, and microbiological (blood urine, sputum, and catheter cultures) monitoring
4. The characteristics of inflammatory fever secondary to acute aortic dissection are:
 - Maximum daily temperature ≥ 37.8 and $< 39^{\circ}\text{C}$
 - The patient has a type B dissection (no surgery performed) or a type A dissection (surgery performed), but with a residual dissection distal to the prosthetic material
 - Fever begins 48-72 h after clinical symptoms of dissection
 - Fever lasts more than 96 h
 - Variation in daily temperature $< 1.2^{\circ}\text{C}$
 - Patient is in "good general condition"
 - Neither anamnesis, physical exploration, cultures nor chest x-rays suggest an infectious process
 - Fever does not remit after 48 h with antibiotics
5. In patients who meet the criteria of point 4, the suspension of antibiotic treatment should be considered and anti-inflammatory therapy contemplated. An early response (< 24 h) to anti-inflammatory therapy indicates fever is secondary to the dissection

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