● Original Article ●

C-reactive Protein in Prognosis of Chronic Aortic Dissection

Keiko Takahashi, and Mitsumasa Ohyanagi

Abstract: *Objective:* To examine a correlation between the clinical prognosis and inflammatory reaction in aortic dissection. *Design:* Twenty-six patients who underwent medical treatment for chronic aortic dissection were divided into the high risk group (H) of 7 patients with a progressive focus on the chronic phase, and the low risk group (L) of 19 patients without progressive focus. The patients were monitored using their hematological findings and inflammatory scintigraphy (In-WBC). *Results:* No change was observed in the C-reactive protein (CRP) values during the acute phase in both groups. However, during the subacute phase, the CRP values in the high risk group were significantly higher than those in the low risk group ($p<0.05$). In-WBC results revealed that a persistent positive accumulation remained during the chronic phase in all high risk patients. *Conclusion:* Monitoring the changes in CRP and In-WBC in all phases can provide prognostic information about treatment planning. (J Jpn Coll Angiol, 2005, **45**: 241–246)

Key words: aortic dissection, C-reactive protein, prognosis

Introduction

The prognosis of chronic aortic dissection lies in the existence of thrombus blockage and in the degree of blood pressure control of the false lumen,[1] among other prognostic factors reported. The incidence of aortic dissection increases with age. Despite advances in diagnostic techniques, the mortality in the acute phase in Japan is substantially high.[2] In the chronic phase, computed tomography (CT) and magnetic resonance imaging (MRI) are used for follow-up.[3]

In the acute phase, type A aortic dissection requires immediate operative intervention. In acute type B aortic dissection, treatment consists mainly of anti-hypertensive therapy and bed rest.[4, 5] In addition, cases needing surgery in the subacute phase and those with lesion progression in the chronic phase are also included in the acute type B aortic dissection group.[6] Therefore, if conservative treatment is chosen for aortic dissection cases, the diagnosis in the acute phase as well as the prognosis in the chronic stage must be determined for the patients. In our reported chronic aortic dissection case, indium-111-oxine labeled leukocyte scintigraphy (In-WBC) documented continuing inflammation in the aortic wall, and the aorta dissected in the chronic phase. Thus, we propose positive scanning for the possible prognostic value.[7]

This report further examined the capability of C-reactive protein (CRP) and In-WBC to produce prognoses and determine treatment for patients with chronic aortic dissection.

Methods

Patient selection

Twenty-six patients who underwent medical treatment for chronic aortic dissection fit in DeBakey's classification type IIIb (IIIb). They were further classified into a high risk (H) group with progress in aortic dissection and a low risk (L) group with no lesion progress. Group H consisted of 7 patients (4 had false lumen extensions, 2 had a retrograde dissection and 1 had a sudden death, F:M = 2:5, mean age = 66.1 ± 5.3) and the low risk (L) group 19 patients with no

Department of Internal Medicine, Division of Coronary Heart Disease, Hyogo College of Medicine, Hyogo, Japan

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lesion progression (F:M = 7:12, mean age = 66.8 ± 4.1). For each patient, their course in the chronic phase, their progression of symptoms in the acute phase, the condition of their false lumen on CT, and the inflammatory reaction in the blood over time were compared. These were further compared with the hematological findings for 10 patients (5 high risk and 5 low risk) who performed In-WBC in the subacute and chronic phases. Written informed consent was obtained from all patients.

Patient's characteristics

The following in all cases were compared: hospitalization, the leukocyte, CRP values, normalization days of inflammatory reactant and the CT findings of the condition of the false lumen over time.

Indium-111-oxine labeled leukocyte imaging protocol

The labeling was conducted using autologous leukocytes as per the method of Thakur et al.[8] In the separation labeling of the actual leukocytes, since this indicates not only the acute phase of inflammation but also chronic persistent inflammation, all leucocytes except neutrophils were labeled and followed by mixed labeling, as per our previous method.[7] The degree of leukocyte labeling was calculated as (cell-associated activity) / (total activity) × 100%.

Approximately 18.5 MBq of labeled leukocytes were infused into the patient, and imaging was carried out 48 hours later using a Starcam 3000XCT gamma camera (General Electric, Milwaukee, WI, USA). Anterior and posterior whole-body views were acquired for 15 min each. A medium energy collimator was utilized. While the images of some patients acquired at 24 hrs. failed to identify differences between blood pools, those acquired at 48 hrs. identified the structures.

Data analysis

Accumulation of indium-111-oxine-labeled leukocytes was confirmed visually from the scintigraphs, and graded as either negative or positive. In conforming to the standard of our hospital, the normal value of CRP was set to be under 0.3 mg/dl. The mean (± SD) peripheral blood leukocyte count and C-reactive protein (CRP) concentration were determined over time. Dunn's procedure (a multicomparison procedure) was used for statistical analysis. A value of $p<0.05$ was considered statically significant.

Results

Patient's characteristics

In acute phase, antihypertensive therapy and bed rest constituted the main treatment which was carried out in all cases. Hospitalization of the high risk group lasted for 34 ± 3 days, while that of the low risk group lasted for 28 ± 5 days, which was short and statistically significant ($p<0.05$). Patients with a confirmed false lumen on repeated CT required the same number of hospitalization days. We found no correlation between the progress of aortic dissection in chronic stage and the condition of the false lumen (**Table 1, 2**).

The blood inflammatory reaction

At admission, the leukocyte and CRP values were measured and kept track over time. The average number of days to normalize these values were different (**Table 3**), whereas the leukocyte values did not show any differences between the high and low risk groups. There was no difference in the CRP values in the acute phase. CRP values were significantly higher in the high risk group during the subacute phase. The CRP continued to be high level as the high risk group entered the subacute phase (**Fig. 1, 2**).

Indium-111-oxine labeled leukocyte imaging protocol

In-WBC was performed in 10 patients. One patient of the low risk group had positive accumulation in the subacute phase while, no patients had positive accumulation in the chronic phase. All 5 patients of the high risk group had a positive accumulation of In-WBC both in the subacute and chronic phases (**Fig. 3, 4**).

Discussion

We examined the relationship between the blood inflammatory reaction and the prognosis of chronic aortic dissection in type IIIb medically treated patients. We continued the documenting increasing CRP values into the subacute phase in the high risk group in which there was lesion

Table 1 Clinical characteristic of patients in high risk group

No.	age (y.o.)	gender	In-WBC	prognosis	false lumen
1.	77	M	+	retrograde dissection	thrombosed
2.	63	M	+	progress	thrombosed
3.	67	M	+	rupture (sudden death)	thrombosed
4.	72	M	+	progress	patency
5.	55	F	+	retrograde dissection	patency
6.	77	F	none	progress	patency
7.	52	M	none	progress	patency

In-WBC+/–, positive/negative accumulation of inflammatory scintigraphy;
none, In-WBC was not carried out

Table 2 Clinical characteristic of patients in low risk group

No.	age (y.o.)	gender	In-WBC	false lumen
1.	60	M	+	thrombosed
2.	71	M	–	thrombosed
3.	66	M	–	thrombosed
4.	54	M	–	thrombosed
5.	62	F	–	thrombosed
6.	70	M	none	thrombosed
7.	80	M	none	thrombosed
8.	59	M	none	thrombosed
9.	66	M	none	thrombosed
10.	68	M	none	thrombosed
11.	67	M	none	thrombosed
12.	73	M	none	patency
13.	71	M	none	patency
14.	58	F	none	patency
15.	60	F	none	patency
16.	77	F	none	patency
17.	78	F	none	patency
18.	71	F	none	patency
19.	60	F	none	patency

In-WBC+/–, positive/negative accumulation of inflammatory;
none, In-WBC was not carried out

Table 3 Normalization days of inflammatory reactant

	white blood cell count	C-reactive protein
H group (day)	5.1±2.9*	34±6**
L group (day)	4.5±2.4	27±1

*n.s. vs. L group, **$p<0.05$ vs. L group

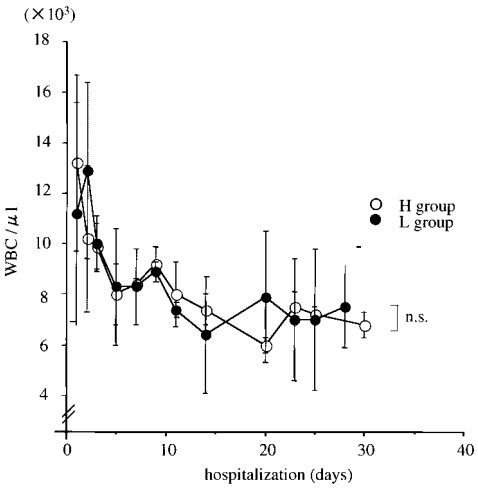

Figure 1 Time dependent of leukocyte concentration. There is no significant change between H and L groups.

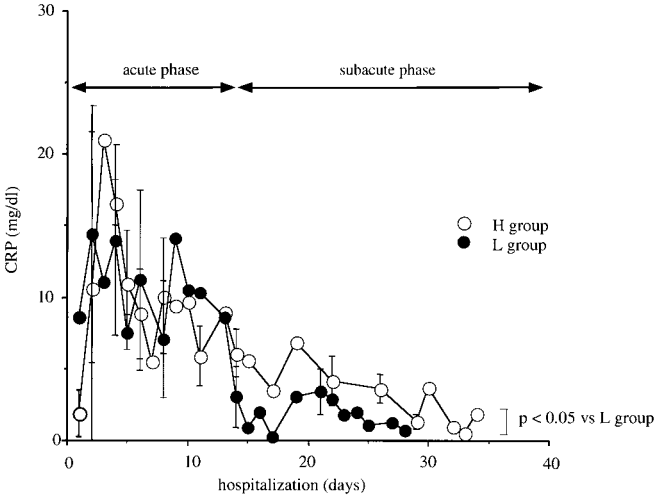

Figure 2 Time dependent of CRP concentration. In the H group, CRP concentration is significantly higher than the one in the L group in subacute phase.

progression in the chronic phase. Furthermore, these patients also had a documented positive accumulation in the aorta of In-WBC. Although mortality is low in type I and type A patients,[9] placement in the type IIIb group does not necessarily offer a good prognosis,[10] especially when the chronic phase outcomes are included. As the standard guidelines fail to give consideration to the long-term prognosis of type IIIb cases, the advised treatment plan for these patients with aortic dissection is not fully effective. Therefore, indices that can predict the possibility of dissection in type IIIb cases are of interest.

Atherosclerosis-related aortic dissection is reported to differ from the regular aortic dissection. Additionally, patients with this lesion have a high risk of developing more dissection from the new site of entry in the same lesion.[11] Though arteriosclerosis has been implicated in the etiology of aortic dissection,[12] whether there is a direct causal relationship between them remains unclear.[13] In our previous report on aortic dissection, arteriosclerosis was not clearly implicated,[7] despite that we observed structural disorganization and inflammatory cell invasion. This is considered to be the mechanisms of the inflammation in the inflammation scintigraphy image.[7] Therefore, the inflammation of aortic dissection is apparently induced by mechanical inflammation, which cases inflammation to continue as documented by inflammation scintigraphy.

The presence of an inflammatory reaction has already been reported in aortic dissection and impending dissection of an aortic aneurysm in the acute phase. These cases marked the elevated inflammatory response, which was linked to acute aortic disease.[14] Our data from the subacute phase suggests that CRP is high in patients with a high risk of aortic disease in the chronic phase, which is a marker of the blood inflammatory response. Rohde et al. reported that the chronic inflammation continues, even in subclinical cases as measured by cytokine blood levels in an abdominal aneurysm.[15] Thus, the continuing inflammation of the aortic wall initiated in the acute phase possibly results in the degeneration of the aortic wall, as reported by McMillan et al.[16] This possibility is substantiated by gated-inflammation scintigraphy and CRP cytokine complement results.

Our data indicates that all the patients in the group whose lesions progressed during the chronic phase, generated persistently high CRP values, as well as accumulation of In-WBC, as documented by inflammation scintigraphy. Therefore, these findings indicate that lesions are likely to extend as a result of continuing inflammation even though there may be few symptoms. Jones et al. have reported that

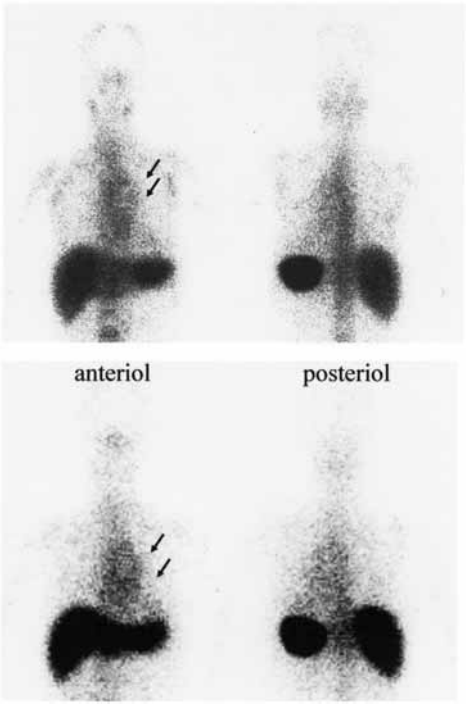

Figure 3 Registered indium-111-oxine leukocyte (In-WBC) imaging: A 55-year-old woman with acute aortic dissection (No. 5 patient of Table 1). In chronic phase she had a retrograde extension of aortic dissection and received the operation. Upper, In-WBC accumulated in the descending aorta at 14 days. Lower, positive accumulation of In-WBC continued in the descending aorta at 54 days.

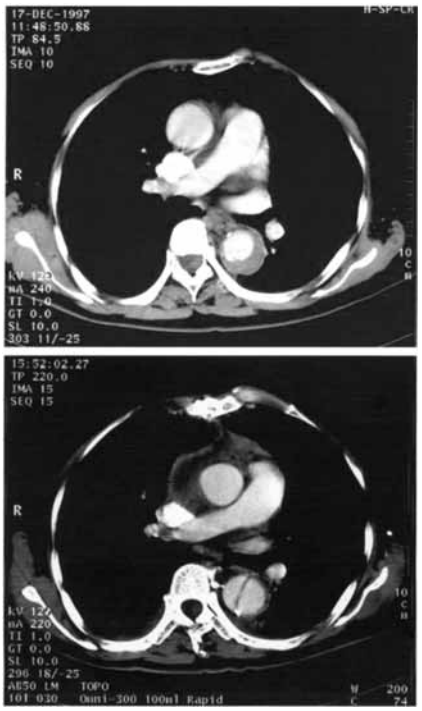

Figure 4 Registered computed tomography (CT) of No. 5 patient of Table 1: Upper, the false lumen was thrombosed at hospitalization. Lower, there were the retrograde extension of aortic dissection at 64 days.

there is a relationship between lesion progression of abdominal aortic aneurysms and blood IL-8 and cytokine levels.[17] Hasegawa et al. have also noted a relationship between the progression of aortic dissection, blood IL-8 concentrations, and the inflammatory reaction.[18] Our findings suggest that CRP and inflammation scintigraphy may also be useful to make a prognosis of lesion progression in the chronic phase. Thus, the simple measurement of CRP in general practice can be of use diagnostically.

As aortic dissection poses a serious risk, prudent observation should be exercised, even in the chronic phase. When lesion develops and diagnosis is made, a patient is already in a precarious and potentially fatal state. Therefore, preventive measures should be considered. The progression of aneurysms can be stopped by suppressing prostaglandin E2 levels and the extravasation of cytokine.[19, 20] In patients with penetrating ulcers and intramural hematomas with aortic dissection, surgical treatment is recommended due to the likelihood of further progression.[21] The need for any preventive measures must be assessed based on the patient's prognosis.

In assessing the likelihood of aortic dissection in the chronic phase, it is useful to note the results of inflammation scintigraphy and CRP values. The need for surgical treatment can be determined by comparing these data to the results reported here.

Conclusion

The follow-up for aortic dissection entails diagnostic imaging up to the chronic phase. Specialized inflammation scintigraphy will be able to show if inflammation has spread to the inside of the aorta, while other modalities cannot accurately display this. Furthermore, fluctuations in the CRP values from the acute to the subacute phase appear to work as an indicator determining in prognosis.

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