Non Specific Aortoarteritis (Takayasu’s Disease)

An Immunologic and Autopsy Study

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Summary
Large segments of the aorta and its major branches were found to be diseased in 14 autopsied cases of aortoarteritis. Both renal arteries and the left subclavian artery were frequently affected. Superior vena cava thrombosis and thickening of the inferior vena cava were noted in one case each. Tuberculosis was present as small foci in only 3 of the 14 cases.

Angiographic evaluation also revealed thickening and narrowing of diseased segments. The descending thoracic and abdominal aorta and renal arteries were frequently involved. Aneurysmal lesions were infrequent.

Antiaorta antibodies were investigated using 4 different parameters. None of our cases showed their presence. The role of tuberculosis and/or autoimmunity appears unlikely in the etiopathogenesis of aortitis.

Additional Indexing Words:
Antiaorta antibodies Tuberculosis Autoimmunity Thoraco-abdominal aorta Aneurysms Superior vena cava thrombosis Thick inferior vena cava

Non-Specific aortoarteritis originally described from Japan has now been reported from various other parts of the world." In India and other South East Asian countries the thoraco-abdominal segment of the aorta is most frequently affected and is a common cause of renovascular hypertension in the young." Absent radial pulsations and cerebrovascular insufficiency due to aortic arch involvement are the commonest clinical presentations amongst the Japanese."
While the etiology of aortitis is not known, autoimmunity is most commonly implicated in the etiopathogenesis of this disease.\textsuperscript{5,6,7} The aim of this present study is to examine this disease through autopsy findings, angiographic profiles and analysis of sera for antiaorta antibodies in an effort to understand the etiopathogenesis of aortoarteritis. This communication is based on an analysis of 14 autopsied cases and blood samples collected during aortogram studies from 50 additional cases of aortoarteritis.

**Materials and Methods**

Fourteen cases of aortoarteritis confirmed at autopsy have been studied in detail. The aorta and its branches and other blood vessels were analysed for the extent, severity and type of involvement. Gross and microscopic examination of the heart, aorta and its branches, pulmonary vessels and all other viscera was done. Formalin fixed tissues were processed conventionally. Five micron thick sections were cut and stained with hematoxylin and eosin. Masson's trichrome, Verhoff's Van Gieson and Alcian blue PAS stains were used on selected sections only.

Fresh normal aortae obtained from medico-legal post-mortems and diseased segments of aorta from 2 autopsied cases of aortoarteritis were collected. Three to 4 micron thick sections of the aorta were cut in the cryostat ($-20^\circ$C) and stored for immunofluorescence studies. Indirect immunofluorescence was done using normal and diseased segments of aorta, patients' sera and FITC tagged anti-human globulin. To identify immune complexes, sections from normal and diseased aorta were treated with FITC tagged anti-human immunoglobulin only. Sections of the aorta were also tested for auto fluorescence.

In addition, 50 cases of radiologically confirmed aortoarteritis who underwent vascular studies were examined. Sera from these patients were stored at $-70^\circ$C and later examined for the presence of antiaorta antibodies. A detailed analysis of the angiographic profile of 42 of these 50 patients was also made.

Antiaorta antibodies were examined by (a) Ouchterlony's gel diffusion,\textsuperscript{8} (b) complement fixation test (CFT),\textsuperscript{9} (c) indirect hemagglutination test (IHA),\textsuperscript{10} and (d) direct and indirect immunofluorescence.\textsuperscript{11} Antinuclear factor (ANF) and anti-smooth muscle antibodies were also determined using indirect immunofluorescence. In addition, the sera were also examined for the presence of C-reactive proteins (CRP) and rheumatoid factor (RH factor) by using test kits provided by Behring Werke, Germany. Titres of Antistreptolysin O (ASLO) were also determined in the sera.\textsuperscript{12}
Another 205 cases who underwent angiographic studies for vascular disorders other than aortitis were also analysed using the above parameters. These included cases of essential and secondary hypertension (41 and 25 cases, respectively), renovascular hypertension (13), Burger’s disease (11), liver diseases (16), vascular disorders such as arteriovenous malformations, aneurysms, atherosclerosis and coarctation of aorta, etc (33), endocrine disorders (14), kidney tumours (22), and 30 cases having miscellaneous diseases. In addition, samples from 16 healthy kidney donors served as controls.

Aorta antigen was prepared by the method of Ueda et al (1967). The protein content of the supernatant extract was determined spectrophotometrically (12 mg/ml) and stored at -20°C in sterile tubes. It was diluted with saline and used as antigen.

Antiaorta antibodies were raised in rabbits. Rabbits were immunised subcutaneously with a 2 ml emulsion consisting of equal parts of aortic antigen and Freund’s complete adjuvant weekly for 5 weeks followed by a single injection of antigen without adjuvant in the 6th week. Rabbits were bled every week and serum was tested for the presence of antiaorta antibodies by gel diffusion as well as IHA test. The titre at the end of the immunisation schedule was 1:512. The precipitation test was also positive.

The aorta antigen and the antiaorta antibodies raised in rabbits were used in performing the various tests for detection of antiaorta antibodies in the patients’ sera. The sera raised in rabbits served as positive controls.

**Results**

1. Autopsy: The 14 patients with aortitis who came to autopsy ranged in age from 11 to 65 years. Five patients were under the age of 20 years. There were equal numbers of males and females.

   Clinically the commonest presentation was hypertension and/or its sequelae. One patient presented with features suggestive of coarctation of the aorta. Erythrocyte sedimentation rate (ESR) was elevated in only 3 patients. LE cell phenomenon, VDRL, Mantoux and Rose Wealer tests were carried out only in some cases and were found to be negative.

   Multiple segments of the aorta and several of its proximal branches were affected by the disease process (Fig. 1). In all cases but 1, the disease segments were markedly thickened and narrowed. Aneurysmal lesions were rare. In 1 case there was a mild dilatation of the ascending aorta while in another case there were multiple aneurysmal dilatations of the aorta with a rupture of one of these into the second part of the duodenum.

   There was a marked thickening involving all the layers of the blood ves-
Fig. 1. Diagram of the aorta and its major branches showing the distribution of the affected segments. The figure on the left (1a) depicts lesions as seen on angiographic evaluation of 42 patients and the one on the right (1b) is based on autopsy analysis of 14 cases. Numbers indicate the frequency of involvement of the aorta and its major branches. INN=innominate artery; RSCA and LSCA=right and left subclavian arteries; RCCA and LCCA=right and left common carotid arteries.

sels. On transverse section of the vessels the lumen was seen to be appreciably narrowed. The intima in most of the cases was severely thickened and intimal lesions of variable size were seen as raised, smooth gelatinous or pearly white patches with intervening scarring. Superimposed atherosclerotic changes were frequent. Organizing thrombi were also seen on the intimal surface.

The descending thoracic segment of the aorta and the abdominal aorta bearing the renal arteries were frequently affected (Fig. 1). Subclavian arteries were also commonly diseased and pulmonary arteries were involved in 2 cases. Similar focal thickening of the left atrial endocardium was also noted in 1 case. In another case there was marked thickening of the inferior vena cava due to medial hypertrophy. Thrombotic occlusion of the superior vena cava was noted in 1 patient. The aortic valve was found to be involved in 3 cases. In 1 case only, severe involvement of the arch vessels was seen along with involvement of other arterial segments as well. This patient had presented with peripheral pulseless disease. Isolated arch involvement was not present in any of our cases. In 2 cases the coronary artery ostia were narrowed due to the disease process.

Infarctions of the lungs and kidneys were frequently encountered. One of the cases of aortoarteritis had an associated retroperitoneal fibromatosis. The incidence of tuberculous infection in this autopsy series was insignificant. In only 3 of the 14 cases were small foci of tuberculosis seen in the lung and/or
tracheobronchial lymph nodes. Tuberculous paraortic lymph nodes were not seen in any of the cases.

Microscopic examination of sections from diseased segments of the aorta showed that there were variable degrees of thickening of all the layers. The adventitia showed mild to moderate fibrosis and increased prominent vasa vasora. Mild chronic inflammatory cell infiltration consisting of lymphocytes and a few plasma cells located perivascularly were noted in the adventitia and outer 1/3–1/2 of the media. The most striking change was a moderate to severe destruction of the media with replacement by large foci of fibrosis. In only 1 case was ill formed epitheloid cell granulomas with occasional giant cells seen. Otherwise, in none of the other cases did we observe frank necrosis or florrid granulomatous response in the media. The intima was variably thickened and showed intense basophilia which was confirmed to be rich in acid mucopolysaccharides.

2. Serological studies: Of the 50 patients with aortoarteritis who were assessed radiologically 28 were males and 22 were females. Two thirds of the patients were below the age of 25 years and the majority of these patients were hypertensive. Angiographic evaluation of the aorta was done in 42 of the 50 cases. Obstructive lesions of the aorta were widespread and several blood vessels were affected. The affected segments were generally thickened and narrowed in the process. Aneurysmal lesions were infrequent and were present in only 4 cases. The aortic segment bearing the renal arteries and the subclavian arteries were most frequently involved (Fig. 1).

Raised ASLO titres were seen in only 13 out of 48 patients with aortitis. Elevated titres were also noted in 4 out of 10 cases of Burger's disease. CRP were present in 19 of 46 cases of aortitis and 6 of 11 cases of Burger's disease. In contrast, most of the cases of aortitis were negative for RH factor in their sera. ESR was elevated in 30 patients. Of the 21 patients subjected to Mantoux testing only 7 showed increased tuberculin sensitivity. Routine radiological examination of the chest did not reveal any parenchymal lesions or mediastinal lymphadenitis in any of the cases of aortitis.

Antiaorta antibodies were not detected in the sera of any of the 50 cases of aortitis diagnosed angiographically or from sera collected from 2 cases at autopsy by any of the four parameters employed by us, namely immunodiffusion, indirect and direct immunofluorescence, CFT or IHA.

**Discussion**

Aortoarteritis classically affects females in the younger age group. In our series, however, although the disease affected the young predominantly,
it was equally prevalent in both sexes.

Autopsy data revealed some unusual sites of involvement. In 1 case gross lesions identical to those in the aortic intima were seen in the intima of the pulmonary trunk and left atrial endocardium. Such lesions have been noted previously by Chhetri et al.\textsuperscript{15)} Associated changes in the venous system are reported to be rare. Schrire and Asherson (1964)\textsuperscript{16)} reported thrombotic occlusion of the inferior vena cava in 1 case. In one of our autopsied cases the superior vena cava was occluded by a thrombus and in another the inferior vena cava was markedly thickened and was "arterialised".

The etiology and pathogenesis of aortitis remain obscure and therefore speculative. It has been postulated that the aorta is rendered autoantigenic by a preceding infection which may be bacterial, viral or tuberculous in nature.\textsuperscript{17)} Circulating antiaorta antibodies have been reported in cases of aortitis.\textsuperscript{5)-7),18)-21)} These have been demonstrated by using CFT,\textsuperscript{5)} IHA,\textsuperscript{20)} and indirect immunofluorescence.\textsuperscript{22)} In spite of using all these procedures we were unable to detect any circulating antibodies against either normal or diseased aorta. Several other studies have also refuted the role of antiaorta antibodies in the pathogenesis of aortitis.\textsuperscript{23)-26)}

Elevated titres occur in the acute phase of the disease and either decrease or disappear after treatment with steroids.\textsuperscript{7)} This fact is also brought out in experimental aortoarteritis where the titres of antiaorta antibodies of sensitised rabbits reached peak values within 3 months from the onset of experiments. Development of arterial lesions was seen only after this period, suggesting thereby that the arterial lesions possibly are an effect rather than a cause of a specific antigen-antibody reaction.\textsuperscript{21)} Thus, our cases may represent an end stage of an earlier acute process, and for that reason, we were unable to detect the presence of antibodies. It is possible that one may be able to detect antibodies if the disease is investigated in its initial stages. Diagnostic criteria for the acute phase of the disease, however, are ill understood and not clearly defined.

Although an association between tuberculosis and aortitis has been suggested,\textsuperscript{27)} we could not detect significant tuberculous infection\textsuperscript{2)} in any of our 14 cases. Some recent studies have indicated that genetic factors may play a role in the etiopathogenesis of aortitis.\textsuperscript{28)}

Microscopically, we did not observe florid granulomatous inflammatory response with giant cells.\textsuperscript{14),29)} Most of our cases showed severe fibrosis of all the walls of the aorta with minimal inflammation. Nasu (1976),\textsuperscript{29)} however, has also stated that in autopsy studies dense fibrosis with scant cellular infiltration is the most frequent finding.

Aneurysmal lesions were encountered in only 1 case at autopsy. In this
case, multiple saccular aneurysms containing organising thrombi were present over the entire length of the aorta. An aorta-enteric fistula was also present. Multiple aneurysms are most commonly described in South African children; however, among all the reported cases of South African aortitis with multiple saccular aneurysms, not a single case showed an aorto-enteric fistula.

The etiopathogenesis of aortitis is undetermined at present. From the autopsy and clinical data in this study the role of tuberculosis as a cause of aortitis appears remote. Autoimmunity also appears unlikely as investigations for antiaorta antibodies gave negative results. Aortoarteritis, however, has certain clinical and laboratory parameters akin to those found in rheumatoid arthritis, rheumatic fever and temporal arteritis. Involvement of the aorta in these diseases as well as aortitis may possibly be due to a similar basic disorder of the connective tissues.

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REFERENCES