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Concise report

Chronic periaortitis with thoracic aorta and epiaortic artery involvement: a systemic large vessel vasculitis?

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Abstract

Objective. Chronic periaortitis (CP) is a rare disease characterized by fibro-inflammatory tissue surrounding the abdominal aorta and the iliac arteries. Anecdotal reports have shown that CP may also involve other vascular districts, particularly the thoracic aorta. The aim of this study was to investigate the thoracic aorta and epiaortic artery involvement in CP.

Methods. Patients were eligible if they had undergone imaging studies assessing inflammatory involvement of the thoracic aorta and its major branches (e.g. contrast CT, MRI or PET-CT). We explored the patterns of thoracic vessel involvement and compared the clinical characteristics of patients with and without thoracic disease. Where available, we also reviewed the thoracic vascular/perivascular tissue biopsies.

Results. Of 153 CP patients seen between 1999 and 2012, 77 were eligible. Of these, 28 (36%) had thoracic involvement: 15 (54%) had thoracic periaortitis, with 7 also showing epiaortic artery involvement; 6 (21%) had periaortitis surrounding a thoracic aortic aneurysm, 2 of them with epiaortic artery involvement; 7 (25%) had a thoracic aortic aneurysm without periaortitis. Patients with thoracic disease were more frequently female ($P = 0.01$), were older ($P = 0.001$) and had a higher frequency of pain and constitutional symptoms ($P = 0.02$). Thoracic (peri)vascular biopsies revealed adventitial and peri-adventitial fibro-inflammatory patterns similar to those observed in abdominal CP.

Conclusion. In about one-third of patients, CP also involves the thoracic aorta and the epiaortic arteries, which supports the hypothesis of a systemic inflammatory disease of the large arteries.

Key words: vasculitis, periaortitis, retroperitoneal fibrosis, giant cell arteritis, aorta, aneurysms.

CLINICAL SCIENCE

Rheumatology key messages

- In one-third of patients, chronic periaortitis involves the thoracic aorta and/or the epiaortic arteries.
- Chronic periaortitis patients with thoracic aorta involvement are more frequently symptomatic, female and elderly.
- Chronic periaortitis with thoracic aorta involvement has features of a systemic large vessel vasculitis.

Introduction

Chronic periaortitis (CP) is a rare disease characterized by fibro-inflammatory tissue spreading from the abdominal aorta and the iliac arteries into the surrounding retroperitoneum. CP includes non-aneurysmal [idiopathic retroperitoneal fibrosis (IRF)] and aneurysmal forms [inflammatory abdominal aortic aneurysms (IAAAs), perianeurysmal retroperitoneal fibrosis (PRF)] [1–3]. Histology reveals pronounced fibrosis and a chronic inflammatory infiltrate [4],

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and in some cases IgG4$^+$ plasma cell infiltration, which is why CP is included in the spectrum of IgG4-related disease (IgG4-RD), a newly recognized condition that often involves other sites (e.g. pancreas, salivary glands) [5].

CP was initially thought to result from a localized inflammatory response to aortic atherosclerotic plaque antigens [3], but recent findings including the association with other autoimmune diseases and with HLA-DRB1*03 and the presence of systemic clinical manifestations [2, 6] suggest a systemic immune-mediated origin. This hypothesis is reinforced by descriptions of CP involving not only the abdominal aorta, but also other vascular areas (e.g. thoracic aorta) [7, 8]. We here explored the frequency and patterns of involvement of the thoracic aorta and epiaortic arteries in CP patients and investigated whether CP with thoracic vessel involvement represents a distinct disease form.

Patients and methods

Eligibility criteria, imaging and laboratory examinations

Between 1999 and 2012, 153 consecutive CP patients were seen at our centre. CP was diagnosed by abdominal CT or MRI, following commonly accepted criteria [9]. When available, whole-body [^{18}F]fluorodeoxyglucose (^{18}F-FDG) PET was also performed. Retroperitoneal and/or abdominal aortic biopsies were performed in patients undergoing ureterolysis or aortic aneurysmectomy and in those with atypical disease localization. Patients underwent routine clinical and laboratory examinations including ESR, CRP and a panel of autoantibodies [10]. IgG4 levels (normal, 8–140 mg/dl) were assessed in a fraction of patients, as this test became available at our centre in 2007. We excluded secondary causes of retroperitoneal fibrosis (e.g. drugs, malignancies, Erdheim–Chester disease) [11], genetically determined diseases causing aortic aneurysms (e.g. Marfan's, Turner's and Ehlers–Danlos syndromes), infectious aortitis, GCA and Takayasu's arteritis (TA) [12].

CP patients were eligible for this study if they had appropriate imaging studies examining the inflammatory involvement of the thoracic aorta and its major branches, which included contrast-enhanced chest CT or MRI and whole-body ^{18}F-FDG PET-CT. CT was performed with a multidetector scanner (1 mm sections) before and after contrast medium injection in arterial and venous phases. Chest MRI studies were performed with a 1.5T MRI system using a phased array torso coil. We examined axial T1- and T2-weighted, fat- and non-fat-suppressed imaging sequences. A T1-weighted three-dimensional gradient echo sequence in the axial plane was performed with fat suppression 35 and 90 s from the beginning of contrast injection. The radiologist evaluated the presence of the perivascular tissue, its thickness, MRI/CT features and contrast enhancement using a region of interest. The aortic diameter was measured (not including the vessel wall) using multiplanar reformatted imaging. On PET, vascular FDG uptake was graded using a 4-point scale: 0, no uptake; 1, low-grade uptake (lower than liver uptake); 2, intermediate-grade uptake (similar to liver uptake); and 3, high-grade uptake (between liver and cerebral uptake or similar to the uptake in the cerebral cortex). Scores of 0–1 were considered negative, while scores of 2–3 were considered positive. The study was approved by the ethics committee of the University Hospital of Parma (Comitato Etico per Parma). All participants signed an informed consent form. Privacy was preserved through the adoption of alphanumeric codes as identifiers.

Histological analysis of CP biopsies

Retroperitoneal or abdominal aortic biopsies and, when available, thoracic aorta or carotid artery biopsies (in patients undergoing aortic aneurysmectomy or carotid endarterectomy) were analysed for diagnostic purposes as previously described [4]. The slides were stained using routine techniques [4]. The degree of IgG4$^+$ plasma cell infiltration was assessed by calculating the IgG4$^+$:CD138$^+$ cell ratio [11].

Statistical analysis

Categorical data were reported as proportions and compared by Fisher's exact test. Continuous data were reported as mean (S.D.) or median [interquartile range (IQR)] and compared by Student's *t*-test or Mann–Whitney test as appropriate. A two-sided *P*-value <0.05 was considered statistically significant. All analyses were done using SPSS 20.0 (SPSS, Chicago, IL, USA).

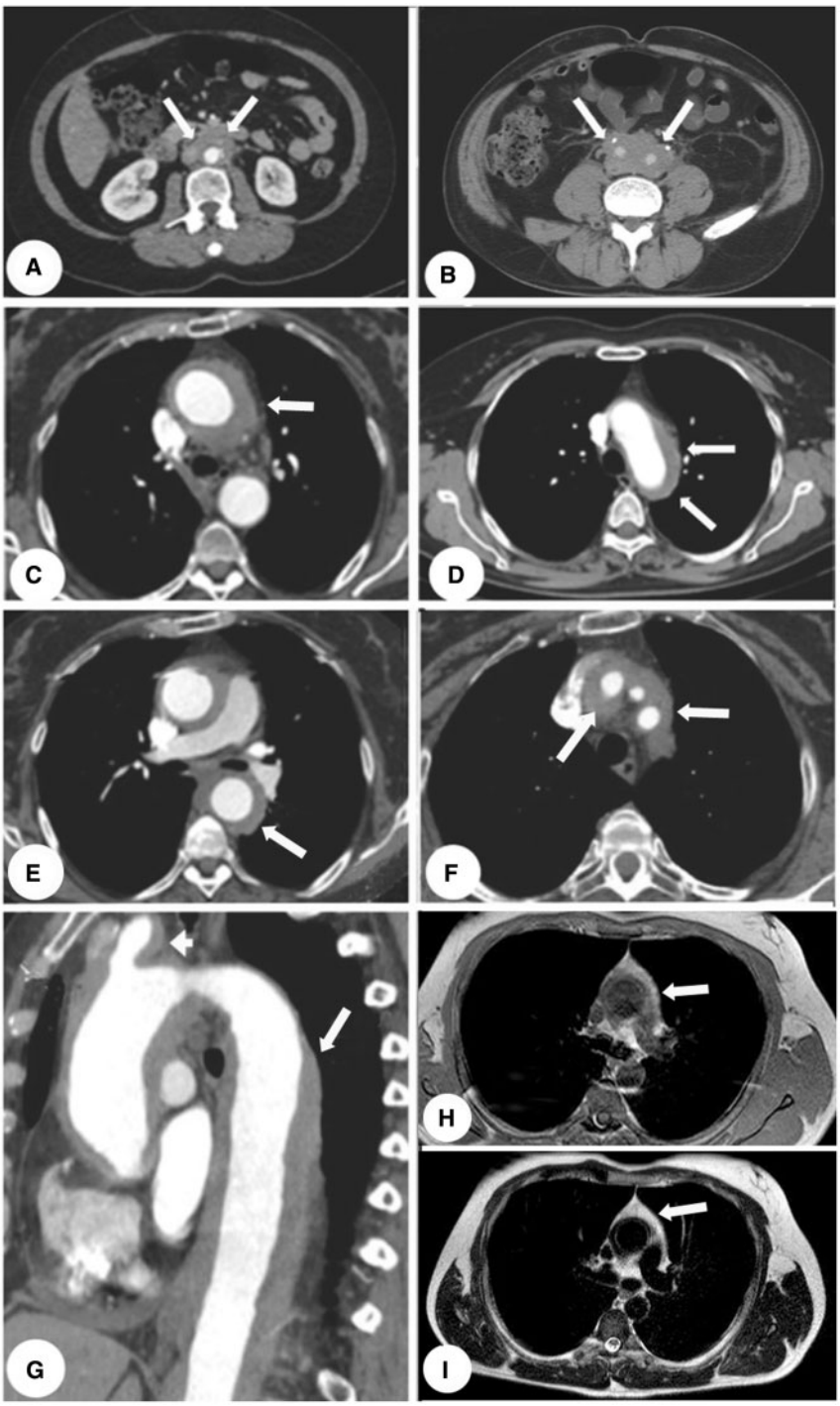
Results

Thoracic vessel disease patterns in CP

Of the 153 patients screened, 77 were eligible for this study; 69 had IRF (Fig. 1A and B) and 8 had IAAA/PRF. Twenty-eight cases (36%) showed thoracic aorta and/or epiaortic artery involvement; this was diagnosed in 9/28 cases by contrast chest CT, in 4/28 by contrast MRI (2 completed the examination with contrast-enhanced magnetic resonance angiography) and in 15/28 by ^{18}F-FDG PET-CT.

In these 28 cases, the following patterns of thoracic vessel involvement were identified (Fig. 1). Thoracic periaortitis (15/28 patients, 54%) had the hallmark of a perivascular soft tissue mass surrounding a thoracic aorta of normal calibre. The tissue was usually homogeneous with no infiltrative features. On non-enhanced CT, its density was similar to that of the thoracic wall muscles. The tissue had low signal intensity on T1-weighted MRI, whereas on T2-weighted scans the signal intensity was usually high. The perivascular tissue enhancement was variable on CT/MRI, probably reflecting disease activity: it was early and avid during active phases and non-significant during inactive phases. On PET, the median ^{18}F-FDG uptake grade was 3+ (IQR 3–4+) around the abdominal aorta and 3+ (IQR 3–4+) around the thoracic aorta. In 13/15 cases with thoracic periaortitis the perivascular tissue surrounded the ascending aorta, the aortic arch and the upper descending aorta (Fig. 1C–E and G–I), whereas in

Fig. 1 Imaging findings in chronic periaortitis patients with thoracic aorta involvement



(**A**) CT appearance of non-aneurysmal chronic periaortitis (idiopathic retroperitoneal fibrosis). A soft-tissue density mass surrounds the anterior and lateral sides of the abdominal aorta (arrows). (**B**) The periaortic mass seen in (**A**) extends to surround both common iliac arteries (arrows) and also encases the ureters where stents are placed. (**C**–**E**) CT appearance of thoracic periaortitis. The perivascular tissue surrounds (**C**) the ascending aorta (arrows), (**D**) the aortic arch (arrows) and (**E**) the upper portion of the descending thoracic aorta (arrow). (**F**) CT appearance of the perivascular tissue that involves the origin of the carotid arteries (arrows). (**G**) Multiplanar reformatted imaging CT appearance of periaortitis in a sagittal view that involves the ascending thoracic aorta (left arrow), the origin of the epiaortic vessels (short arrow) and the descending aorta (right arrow). (**H** and **I**) MRI appearance (T1- and T2-weighted scans, respectively) of thoracic periaortitis. In this patient, perivascular tissue is present around the ascending aorta. The perivascular tissue surrounding the ascending aorta is hypointense in both T1- and T2-weighted scans, reflecting an inactive phase of the disease.

2 cases it involved the lower descending aorta. Seven of 15 patients also showed perivascular involvement of the origin of the epiaortic arteries (common carotid in 5, left subclavian in 1 and brachiocephalic in 1) (Fig. 1F). In thoracic aortic aneurysm with periaortitis [6/28 cases (21%)], the characteristics of the perivascular tissue were similar to those described above, but the thoracic aorta showed aneurysmal dilatation (>50% of the expected normal diameter). Epiaortic vessel involvement was found in two cases (common carotid arteries in both and left subclavian in one). In thoracic aortic aneurysm without periaortitis [7/28 patients (25%)], the aneurysm involved the ascending aorta in 5 cases, the aortic arch and descending aorta in 1, and the ascending aorta, the aortic arch and the descending aorta in 1. We included thoracic aortic aneurysm without periaortitis as a disease-related manifestation because it is a potential complication of large vessel vasculitides.

Thoracic vessel disease was symptomatic in only four patients (14%); in these cases thoracic periaortitis was always associated with epiaortic involvement. Two patients had hoarseness secondary to recurrent laryngeal nerve paralysis. Unilateral deficit in arm strength, asymmetrical pulses/blood pressure values were observed in two patients and arm claudication, upper limb paresthesias and dry cough were found in three patients. Four patients underwent thoracic aneurysm repair (two surgical, two endovascular) and two carotid endoarterectomy.

CP histology

Retroperitoneal biopsies were available in 46% of patients with and 47% of patients without thoracic involvement, whereas thoracic CP biopsies were available in three patients (two after carotid endarterectomy and one after surgical repair of thoracic aortic aneurysm). Histological examination of abdominal biopsies showed a typical CP pattern and no differences in histological features were found in patients with *vs* without thoracic involvement. Histology of the thoracic tissue was strikingly similar to that found in abdominal CP [4]. The pathological lesions in thoracic CP involved the adventitia and the periadventitial tissue and consisted of a fibrous component and a chronic inflammatory infiltrate (supplementary Fig. S1, available at *Rheumatology* Online), as described in abdominal CP [2, 4]. The inflammatory infiltrate displayed perivascular and diffuse patterns and consisted of lymphocytes, histiocytes, plasma cells and eosinophils. The follicular aggregates, often with germinal centres, were rich in lymphocytes, which clustered around adventitial vasa vasorum (Supplementary Fig. S1, available at *Rheumatology* Online). Immunohistochemistry revealed in two of these three cases (one with thoracic periaortitis and epiaortic artery involvement, the other with thoracic periaortitis plus aneurysm) an $IgG4^+$:$CD138^+$ plasma cell ratio >40% (the cut-off used to define CP as IgG4 related) [13].

Demographic, laboratory and clinical features in patients with and without thoracic disease

Patients with thoracic involvement had a significantly higher female prevalence ($P = 0.01$), a greater age at disease onset ($P = 0.001$), a higher prevalence of systemic symptoms (e.g. fatigue, anorexia, weight loss) ($P = 0.02$) and back or abdominal pain ($P = 0.02$) (Table 1). Patients with thoracic disease also tended to have higher ESR and CRP level than patients without thoracic disease, although the differences were not statistically significant. Similar proportions of patients in the two groups had other autoimmune diseases, the most common of which were autoimmune thyroiditis and psoriasis. IgG4 measurement was available in 45/77 patients (58%); serum IgG4 levels (data not shown) and the percentage of patients with high IgG4 did not differ in the two groups (Table 1), so IgG4 did not characterize a CP subset with more frequent extraretroperitoneal lesions, in contrast to previously reported data [13, 14].

Discussion

CP is usually thought to be confined to the abdominal aorta and the iliac arteries and its pathogenesis is considered secondary to a localized inflammatory reaction to atherosclerotic plaque antigens [3, 15]. Our study challenges this view and shows that in one-third of patients it also involves the thoracic aorta and the epiaortic arteries. This may suggest that in such cases, CP actually represents a primary, diffuse inflammatory disease of the aorta and its major branches.

Anecdotal reports have described in CP the occurrence of periarteritis involving large arteries such as the coronary [16, 17], renal, mesenteric and coeliac axis [18]. Interestingly, autopsy studies in CP showed adventitial inflammation in aortic sections (mainly at the thoracic aorta level) lacking periaortic fibrosis, suggesting the presence of widespread aortic disease and implying a transition from adventitial inflammation to fibrosis [7]. Molecular analysis of CP biopsies revealed gene transcripts (IFN-γ, IL-2 and IL-4), indicating lymphocyte activation within the aorta wall [19]. Finally, the pattern of vascular inflammation in CP is also consistent with an inflammatory vascular disease: as in GCA and TA, inflammation in CP predominates in the adventitia. This was seen on abdominal aortic biopsies [3, 10] and also in the thoracic aortic biopsies examined here, where the lymphomonocytic infiltrate typically involves the adventitia and the media–adventitia border. Adventitial vasa vasorum, a possible port of entry for disease-triggering pathogens in GCA [20], are often inflamed in CP; in addition, the observed adventitial germinal centres are the expression of ectopic lymphoneogenesis, a feature of many autoimmune diseases. These findings suggest that CP may arise as a primary large artery inflammatory disease, which in some patients is localized to the abdominal aorta and iliac arteries and in others extends to other vascular segments.

The patterns of large thoracic artery involvement ranged from classic periaortitis—with or without aortic dilatation—to

TABLE 1 Demographic and clinical findings in CP patients with and without involvement of the thoracic aorta and its main branches

	Thoracic involvement ($n = 28$)	No thoracic involvement ($n = 49$)	*P*-value
Female, *n* (%)	14 (50)	10 (20)	0.01
Age, median (IQR), years	64.5 (58.3–69.5)	56 (50–59)	0.001
Non-aneurysmal *vs* aneurysmal CP, *n*	25 *vs* 3	44 *vs* 5	1.00
Biopsy-proven CP (retroperitoneal biopsy), *n* (%)	13 (46)	23 (47)	0.81
Clinical manifestations, *n* (%)			
Abdominal or lumbar pain	26 (93)	33/48 (69)	0.021
Systemic symptoms	24 (86)	28/47 (59)	0.020
Testicular manifestations[b]	3/14 (21)	23/39 (59)	0.12
Deep vein thrombosis	4 (14)	8 (16)	1.00
Constipation	9 (32)	18/48 (37)	0.80
Renal-ureteral involvement, *n* (%)			
Ureteral obstruction			
Overall	21 (75)	32 (67)	0.45
Unilateral	8 (38)	18 (56)	0.26
Bilateral	13 (62)	14 (44)	0.26
Acute renal failure	13 (46)	18 (37)	0.47
Laboratory findings			
ESR, median (IQR), mm/h	72 (47–92)	55 (34.75–89.75)	0.20
CRP, median (IQR), mg/l	22.9 (6.9–44.5)	16.2 (6–43.1)	0.59
Hb, median (IQR), g/dl	11.5 (10.5–13)	12.4 (11.2–13.3)	0.07
WBC, median (IQR),/mm^3	6800 (5720–7355)	7110 (6220–8485)	0.33
Autoimmunity, *n* (%)			
Associated autoimmune or inflammatory diseases	11 (39)	18 (37)	1.00
Positive ANA	4/26 (15)	13/45 (29)	0.26
Other positive autoantibodies[c]	13/26 (50)	14/45 (31)	0.13
High serum IgG4 (>140 mg/dl)	3/13 (23)	7/32 (21)	0.71
CV risk factors and CV diseases			
Fasting glucose, median (IQR), mg/dl	92 (82–99)	90 (85.5–95)	0.12
Total cholesterol, median (IQR), mg/dl	191 (172–214)	197 (162–228)	0.47
No. of atherosclerotic risk factors,[d] median (IQR)	1.5 (1–4)	2 (1–4)	0.31
Established atherosclerotic disease,[e] *n* (%)	7 (25)	17 (35)	0.45

[a]Systemic symptoms include weight loss, anorexia, fever, fatigue, diffuse myalgias or arthralgias. [b]Testicular manifestations include testicular pain, varicocele and hydrocele. [c]Other positive antibodies indicate one or more of the following: RF, ANCA, anti-dsDNA, anti-thyroglobulin, anti-thyroperoxidase, anti-smooth muscle or anti-Ro(SSA)/La(SSB) antibodies. [d]Atherosclerotic risk factors include hypertension, diabetes, BMI $\geqslant 30$, smoking and hypercholesterolaemia. [e]Established atherosclerotic disease comprises ischaemic heart disease, cerebrovascular disease and peripheral arterial disease; these were recorded during the entire follow-up. CP: chronic periaortitis; CV: cardiovascular; Hb: haemoglobin; IQR: interquartile range; WBC: white blood cell.

thoracic aortic aneurysms without periaortitis. All these patterns can be seen in other large vessel diseases, primarily GCA and TA, which often affect not only the epiaortic tree, but also the thoracic and abdominal aorta. GCA and TA usually lack the thick periaortic cuff seen in CP, and GCA features cranial symptoms (e.g. scalp tenderness, visual abnormalities) that are almost absent in CP. However, some GCA and TA patients present with isolated non-specific manifestations, such as systemic symptoms, that make the differential diagnosis more challenging. One distinguishing feature between CP and GCA/TA is ureteral involvement, which is only found in CP [9, 11].

When managing CP patients with thoracic aorta involvement it is mandatory to exclude two other diseases presenting with similar features: Erdheim–Chester disease, a non-Langerhans cell histiocytosis, that presents with symmetrical long bone involvement and often peri-renal fibrosis, and IgG4-RD. Recent reports have shown that CP belongs to the spectrum of IgG4-RD, as both IRF and IAAA are characterized, in ~40–50% of cases, by numerous IgG4$^+$-infiltrating plasma cells [5, 13]. Two of the three thoracic aorta/carotid biopsies available in our patients had significant IgG4$^+$ plasma cell infiltration, suggesting an overlap between CP and IgG4-RD, but these patients lacked involvement of other sites by IgG4-RD.

The comparison of demographic and clinical characteristics of patients with and without thoracic involvement revealed that these subgroups were different. Patients with thoracic disease were more frequently female and

older—characteristics reminiscent of a GCA phenotype—and the frequency of disease-related symptoms was also higher in this group.

In conclusion, in about one-third of patients CP is not limited to the abdominal aorta, but also involves the thoracic aorta and the epiaortic arteries. Active adventitial inflammation is seen in both thoracic and abdominal aorta biopsies, a pattern that suggests that CP may be a primary large vessel inflammatory disease.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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