Critical Coronary Artery Stenosis and Aortitis in a Patient with Relapsing Polychondritis

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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Potential Determinants of Poor Disease Outcome in Socioeconomically Disadvantaged Patients with Rheumatoid Arthritis

To the Editor:

We read with interest the report by Suarez-Almazor and colleagues on the disparities in the time to initiation of disease modifying antirheumatic drugs (DMARD) in patients with rheumatoid arthritis (RA) under public care as compared to those under private care, seen at rheumatology clinics in Texas. The authors reported that the median disease duration at the time of initial DMARD therapy was 1.5 years in the public care setting and 0.5 years in the private care setting (p < 0.0001) and that ethnicity (White vs Non-White) was more important than being under public care (surrogate marker of socioeconomic status) in determining delayed DMARD initiation. The authors conclude that “the potential effects of these disparities on longterm outcomes are unclear, but could be very detrimental in the light of the evidence supporting early onset of DMARD therapy for most patients.” We have recently reported on the timing of DMARD in 359 subjects with RA, 196 public care and 163 private patients, seen in Johannesburg, South Africa. Our results differ from those reported by Suarez-Almazor. Moreover, we recorded not only the timing of DMARD initiation but also the Health Assessment Questionnaire (HAQ-DI), a central outcome variable in RA, as well as lifestyle factors, disease activity and disease severity variables, comorbidities, and treatment characteristics. We therefore believe that our results are of potential interest in the present context. Further, the editorial by Madhok and colleagues accompanying the article by Suarez-Almazor is informative in the interpretation of our results.

Only 11% of the South African population is Caucasian. Yet, 85% of our private care patients belonged to the latter ethnic group, as compared to only 13% of our public care patients with the majority of them being African (62%) and the remainder Asian (12%) or of mixed ancestry (12%). As applied to the patients of Suarez-Almazor, being under public care reflected socioeconomic disadvantage. Tumor necrosis factor-α blockade therapy and leflunomide were not available in our public care clinic. In contrast to Suarez-Almazor’s study, the time to DMARD initiation was not significantly different between public care (1.5 yrs) and private care patients (2 yrs) in our study. However, as well documented in previous RA investigations and as further discussed by Madhok and colleagues, we found that socioeconomic disadvantage was associated with more severe RA. Thus, current disease activity and disease severity scores (number of deformed joints) were substantially and significantly higher in public care patients as compared to private care patients. Being under public care was also associated with the comorbidities of obesity and tuberculosis. These differences in current and cumulative disease activity between public and private care patients were present despite overall equally intensive DMARD prescriptions in both settings. Finally, whereas adverse lifestyle factors contribute to socioeconomic health differences as alluded to by Madhok and colleagues, our public care patients smoked and used alcohol less often than did our private care patients.

In contrast to the finding of Suarez-Almazor, et al, that ethnicity rather than socioeconomic disadvantage predicted the delay in DMARD initiation in multivariable analysis, we found that socioeconomic disadvantage rather than ethnicity predicted poor disease outcome (HAQ > 1). As expected, current and cumulative disease activity were further independently associated with poor disease outcome. Suarez-Almazor and colleagues found that the time to glucocorticoid initiation was also more delayed in socioeconomically disadvantaged patients with RA. Although glucocorticoids may retard radiographic progression when used early in the course of RA, the longterm use of these agents in established RA is not supported by currently available evidence. Of interest in this regard, prednisone therapy, which was used 2.6 times more frequently in the public care setting than in the private care setting, was independently associated with a HAQ > 1.

Studies that address differences in characteristics of patients with RA seen in public care versus those seen in private care settings have the potential to contribute to the understanding of poor disease outcome in this disease. Although recently reported evidence indicates the need for early DMARD therapy with its appropriate regular intensification in the case of ongoing disease activity in RA, we found a poorer disease outcome in socioeconomically disadvantaged patients despite a lack of difference in the time to DMARD initiation as well as in the overall prescription patterns of DMARD. Indeed, the potential causes of poor disease outcome in socioeconomically disadvantaged patients with RA are many, often interrelated and complex. As a consequence of our findings and in view of recently reported evidence in 2005, we established a refractory RA clinic in our public setting in which patients with marked ongoing disease activity are managed separately, seen at more regular intervals, and comprehensively assessed at each visit. Whether tighter disease activity control can be obtained in this manner and in this setting is currently being investigated.

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**Dr. Suarez-Almazor replies**

To the Editor:

We thank Dr. Solomon, et al for their additional contributions to the very important topic of timely access to therapy for patients with RA from disadvantaged backgrounds. Their study and ours are in very different countries, South Africa and the United States; however, both show a delay in onset of therapy for patients with low socioeconomic status.

Our study showed a more marked effect of race in this disparity, which was not observed by Solomon. While the reasons for this discrepancy are not clear, many of our disadvantaged patients in the public County Hospital are Hispanic, often illegal immigrants who in addition, do not speak English. We suspect this may have caused a further delay in seeking care, which we cannot document given the nature of our retrospective review, but could have made the effect of race more prominent than that of healthcare setting alone.

Disparities in the provision of healthcare are pervasive, particularly in countries without universal health insurance. We are encouraged to see this issue being assessed by others. The deleterious effects of a delayed onset in treatment are detrimental. Our community of rheumatologists and patient advocates must continue to raise awareness of the need for universal access to therapy for patients with RA.

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**Infusion Reaction to Infliximab in a Patient with Rheumatoid Arthritis After Discontinuation Over 1 Year and Readministration**

To the Editor:

We read with interest the article by Baraliakos, et al concerning no increase in incidence of infusion reactions after infliximab readministration in patients with ankylosing spondylitis1. In some rheumatoid arthritis (RA) cases, this treatment has to be discontinued due to infusion reactions2. Overall, the incidence of infusion reaction to infliximab is about 5% of cases in Crohn’s disease (CD)3,4, and as recently reported, when combined with glucocorticoid therapy, from 4.6% to 8.6% in RA5. Further, delayed cases in CD were reported in 25% of patients who received infliximab again after a 2–4 year interval without infliximab treatment3.

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Drs. Baraliakos and Braun reply

To the Editor:

We thank our Japanese colleagues for their comments on our study1. Toki, et al describe an allergic infusion reaction in a patient with rheumatoid arthritis (RA) after discontinuation and retreatment with infliximab, and comment on our published experience in patients with ankylosing spondylitis (AS) who had been treated with infliximab for some years before it was discontinued and later readministered. The incidence of allergic and other immunologic reactions in response to infliximab therapy has long been studied. This includes antibody formation (antibodies to infliximab, ATI), low infliximab trough levels, infusion reactions, and loss of response. However, the relationship between laboratory measurements and clinical symptoms has not been impressive2. From early data it became clear that the dosage of infliximab has an effect on antibody formation3. Later, it was found that the hit-and-run strategy that was often used initially in patients with Crohn’s disease was also associated with increased antibody formation and other problems; this was partly attenuated by immunosuppressants4.

The patients in our study had been treated with infliximab without interruption for 3 years4. Thus, this was a highly selected group of responders to therapy. This likely contributed to the low frequency of allergic reactions, since patients who had developed infusion reactions had dropped out earlier.

Further, as mentioned by Toki, et al, the role of ATI with respect to development of infusion reactions is not clear. In our study we found ATI in only one patient (without clinical relevance); this may be explained in part by well known technical problems, such as high levels of infliximab in the serum. Correlation of ATI and clinical symptoms such as infusion reactions and loss of response has been reported in patients who were episodically treated with infliximab for active Crohn’s disease5. The patients in our study had not been treated episodically. However, using a different technique for antibody detection, recent data from The Netherlands have suggested a stronger correlation of ATI and clinical symptoms5.

Finally, infliximab in RA is mainly used and approved in combination with methotrexate (MTX) because of superior efficacy6; this is different in AS, where MTX has no proven clinical efficacy on back symptoms7. In the case reported by Toki, et al the first infusions of the patients were performed in combination with MTX, and it is unclear how long this was continued and which dosage was used. Whether the relatively low dosages of MTX used in Japan8 have the same potency to suppress antibody formation is also unclear.

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Abatacept for Refractory Juvenile Idiopathic Arthritis-Associated Uveitis — A Case Report

To the Editor:

Juvenile idiopathic arthritis (JIA) is a well recognized cause of uveitis in childhood. The overall prevalence of JIA-associated uveitis has been reported to be as high as 34%1. Uveitis is characterized by anterior chamber cellular infiltration and aqueous flare. Severe vision-compromising complications such as cataracts, iritis, band keratopathy, posterior synechiae, hypotony, and glaucoma occur in more than 30% of affected individuals and may result in blindness1.

Topical corticosteroids are the mainstay of treatment for uveitis; however, prolonged topical use may result in cataracts or glaucoma, while protracted systemic use has significant side effects. Treatment options also include disease modifying antirheumatic drugs (DMARD) such as cyclosporine and mycophenolate, and anti-tumor necrosis factor (TNF) agents such as adalimumab and infliximab. TNF-α is an important cytokine in the inflammatory process occurring in children with JIA. Animal model studies have shown that TNF-α mediated inflammation occurs in autoimmune uveitis2,3. While adalimumab has been effective for the majority of patients, no treatment has been 100% successful1,4.
Abatacept is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte antigen 4 (CTLA4) linked to the modified FC domain of human IgG1. It avidly binds to CD80/CD86 on antigen-presenting cells, blocks the CD28 costimulatory signal, and results in T cell inactivation. It has proven effective in patients with refractory rheumatoid arthritis and efficacious and safe in adults. There are no published reports of its use to treat children for uveitis.

A 16-year-old Hispanic girl with psoriatic arthritis and IgA deficiency was diagnosed with uveitis at 5 years of age. Her right eye had normal visual acuity (VA) of 20/20, while her left eye VA was 20/100 with synchia, band keratopathy, and cataract. She was initially treated with topical steroids and beta-blocker ophthalmic drops without improvement.

At 6 years of age, she started taking methotrexate (10 mg/m²) and prednisone 10 mg. Cyclopsorine was added 1 year later because of persistent uveitis with scarring. She required a penetrating keratoplasty for band keratopathy. She was maintained with cyclosporine, methotrexate, both systemic and topical steroids, and a mydriatic for 2 years. Mycophenolate was then added because of progression of the ocular inflammation. Methotrexate was discontinued.

When she was 8 years old, she was taking cyclosporine 5 mg/kg/day, mycophenolate 500 mg twice daily, prednisone 5 mg, and topical steroids. Infliximab infusions were initiated with stabilization of her eye inflammation. She underwent a trans pars plana vitrectomy for severe vitritis and removal of an inflamed vitreous to reduce inflammation.

Infliximab therapy was discontinued after 1 year because of infusion-related dyspnea and tachycardia. She was maintained with prednisone 15 mg, cyclosporine 5 mg/kg/day, and mycophenolate 500 mg twice daily. Four months later, she developed back and shoulder pain and a scalp and nail rash. Skin biopsy revealed findings were consistent with psoriasis, which improved on topical medication. Magnetic resonance imaging of the spine did not reveal disc protrusion, canal stenosis, or nerve root compression.

Her uveitis remained very active. At 10 years of age, cyclosporine was increased to 7 mg/kg/day, and she was maintained with prednisone 15 mg, mycophenolate 500 mg twice daily, and topical steroid drops. Daclizumab 2 mg/kg intravenously (IV) was given monthly for 6 months without response. She received etanercept (0.4 mg/kg/dose twice/wk) for 3 months when she was 11 years old without improvement in her uveitis. Mycophenolate was discontinued and monthly cyclophosphamide (750 mg/m²) was given for 5 months without effect. She then received 2 infusions of rituximab (600 mg/m²) followed 24 h later by cyclophosphamide (750 mg/m²) over 2 weeks.

Although her uveitis initially improved, she had recurrent inflammation 6 months after her first course of rituximab and cyclophosphamide. At that time, she was taking prednisone 2.5 mg, cyclosporine 4 mg/kg, sulfasalazine 500 mg twice daily, diclofenac 50 mg twice daily, and topical steroids. Two additional infusions of cyclophosphamide and rituximab were given 2 weeks apart without sustained improvement.

Because of her continuing active uveitis and risk of permanent bilateral visual loss, abatacept infusions were started at 10 mg/kg IV (500 mg). Infusions were given at 0, 2, and 4 weeks, and every 4 weeks thereafter. There was a rapid decrease in her ocular inflammation and improvement in her eye disease, resulting in reduction of her medication doses to prednisone 5 mg and cyclosporine 2.5 mg/kg, and discontinuation of sulfasalazine and diclofenac. There have been no increased infections or adverse reactions. After 18 months of therapy her uveitis remains well controlled and she has experienced no complications of the abatacept. There is decreased inflammation of her left eye, and the retina can be visualized through her transplantated cornea. Her visual acuity has been maintained at 20/25 bilaterally.

CTLA4-Ig administration inhibits development of organ-specific autoimmune disease in a variety of model systems (e.g., collagen-induced arthritis, autoimmune uveitis, and experimental antiglomerular basement membrane autoimmune glomerulonephritis). Experiments have also shown that blockade of the interaction between the B7 family of cell-surface molecules (CD80/86) and CD28 by CTLA4-Fc reduced the incidence and severity of autoimmune anterior uveitis in experimental models. Although the role of peripheral and intraocular T lymphocytes in uveitis is uncertain, this single observation suggests abatacept may represent a useful new alternative and therapeutic approach for treating patients with refractory autoimmune uveitis.

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Critical Coronary Artery Stenosis and Aortitis in a Patient with Relapsing Polychondritis

To the Editors:
Relapsing polychondritis (RP) is a multisystem autoimmune disease with cartilage inflammation. Cardiovascular manifestations are associated with significant morbidity and mortality. Vasculitis involving the coronary arteries is rare. Our patient developed severe ostial lesions in 2 major coronary arteries and aortitis requiring surgical intervention despite intensive medical treatment.

A 30-year-old male Caucasian dental surgeon developed a painful, swollen left ear in January 2001. He was otherwise asymptomatic. Initial laboratory investigations were normal. A clinical diagnosis of relapsing
polychondritis was made. His ear inflammation resolved after prednisone 30 mg daily for 3 weeks. Over the next 5 years he had 2 further episodes of left ear inflammation, pain and swelling of the bridge of his nose (2002), and uveitis (2003). He did not smoke. There was no family history of cardiac disease.

In the summer of 2006, he developed unaccustomed shortness of breath on exertion, fatigue, a recurrence of his left ear inflammation, and diffuse abdominal pain. Pulmonary function tests and a computed tomography (CT) of the chest were normal. He then complained of chest discomfort while walking progressively shorter distances and was referred for urgent cardiac assessment.

Examination was unremarkable with a blood pressure of 120/80. He was in sinus rhythm and breathing comfortably on room air. His body mass index was 21. There were no lymphadenopathy, or joint, eye, or ear abnormalities. Heart sounds were normal with no murmurs or added sounds. Chest examination was normal with no stridor, wheezing, or crackles.

Laboratory investigations revealed normal erythrocyte sedimentation rate, C-reactive protein, troponin, fasting glucose, C3 and C4 levels, and fasting lipid profile. Antinuclear antibodies, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, rheumatoid factor, and antiphospholipid antibodies were negative, and repeated 12 weeks later. An echocardiogram displayed normal sinus rhythm with Q waves in the inferior leads.

Echocardiogram showed a left ventricular ejection fraction of 53%, mild aortic regurgitation (AR), and normal right ventricular systolic pressure. Cardiac CT showed extensive, asymmetric wall thickening at the aortic root and proximal ascending aorta. There was severe stenosis of the ostium of both right and left main coronary arteries (Figure 1). Cardiac magnetic resonance imaging (MRI) showed subendocardial infarction of the inferior and inferoseptal segments at the base and mid-cavity (Figure 2). Abdominal CT revealed 50% narrowing of the proximal right iliac artery.

He was initially treated with prednisone (1 mg/kg/day), oral methotrexate (titrated up to 25 mg weekly), and a beta blocker. His angina improved over the next several days. He received 3 intravenous infusions of infliximab (5 mg/kg/dose) over the next 2 months. Although he was asymptomatic at 12 weeks into therapy, an exercise stress test (Naughton protocol) was positive. The patient refused early catheterization and surgery in favor of further immunosuppressive therapy. Infliximab and methotrexate were discontinued, and he began taking oral cyclophosphamide 100 mg daily.

Cardiac catheterization and aortography in February 2007 showed critical left main stem ostial disease, modest disease in the mid left arterial descending, and moderate aortic regurgitation. The right coronary artery was too tight to be cannulated. Elective surgery was carried out in April 2007 with triple coronary artery bypass and composite replacement of the aortic valve and ascending aorta. Pathological examination showed the presence of a pan-aortitis with a perivascular infiltrate, predominantly of lymphocytes, macrophages, and few plasma cells (Figure 3).

The patient recovered uneventfully from surgery, remains asymptomatic, and has returned to work. He is being maintained with a tapering dose of prednisone, methotrexate 20 mg weekly, atorvastatin, acetylsalicylic acid (ASA), metoprolol, and coumadin. Echocardiogram 6 months post surgery showed mild improvement in left ventricular function.

Vasculitis is estimated to occur in 11-56%1,2 of patients with RP and has a 5 and 10 year survival probability of 74% and 55%, respectively2. A literature review indicates that aortic valve (AV) involvement occurs in 4–6% of patients with RP, and severe regurgitation is a frequent indication for surgical intervention3. Mortality secondary to cardiovascular manifestations is estimated at 18%, second only to laryngotraechal involvement4,5. Coronary ostial lesions are uncommon and presumed related to involvement of the adjacent aorta. The main histological findings are a lymphocytic infiltration around the vasa vasmorum of the outer media with loss of elastic tissues6. To our knowledge there are only 4 other cases reported in the literature6-9.

Reported medical management of RP with coronary vasculitis has included high doses of corticosteroids, methotrexate, and/or cyclophosphamide3,5. We chose infliximab prior to cyclophosphamide because of anecdotal reports10 and personal success in the treatment of severe RP. Despite aggressive medical management, most patients with cardiovascular involvement require surgical intervention because of severe, irreversible structural damage.

Reported surgical outcomes for cardiac manifestations of RP are limited. Postoperative complications, including prosthetic dehiscence and perivalvular leakage, are in part due to corticosteroid therapy causing aortic tissue fragilization3. It is recommended that all patients...
requiring surgery for disease involving the ascending aorta or sinuses of Valsalva have a prophylactic Bentall-type operation with composite aortic graft, along with coronary button re-implantation technique. All patients need close follow-up because of the relapsing nature of the disease.

The fact that the clinical presentation of cardiovascular manifestations usually occurs late, and there is often no elevation in inflammatory markers, makes it extremely difficult to detect such lesions and to monitor disease activity. A favorable outcome is dependent on awareness, early diagnosis, aggressive medical treatment, and surgical correction when stable.

Figure 2. Cardiac MRI, short axis oblique projection of the basal left ventricle (LV), post gadolinium using a prepared inversion recovery gradient echo pulse sequence. There is a well-defined area of subendocardial enhancement (arrow) in the territory of the right coronary artery, involving 60-75% of the thickness of the infero-septal wall of the LV consistent with subendocardial infarction. RV: right ventricle.

Figure 3A. Surgically excised segment of aorta showing an area of ulceration with a thrombus seen in the base of the ulcerated region. The surrounding aortic intima appears grossly unremarkable. B. Section of aorta from the grossly ulcerated area seen in A. There is a break in continuity of the aorta, with the gap bridged by new fibrovascular tissue (arrow). This area shows thick walled arteries and an infiltrate of mononuclear cells. The adjacent area shows features of panaortitis. I: intima; M: media; Stain: Movat pentachrome, original magnification ×2.5.

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Is Carotidynia Syndrome a Subset of Vasculitis?

To the Editor:

Carotidynia is the syndrome characterized by unilateral neck pain initiated described by Fay in 1927. The clinical finding is tenderness over the carotid bifurcation and pain aggravated by movement of the neck without structural abnormality. The symptom has a short duration of about 2 to 4 weeks, suggesting self-limited disease. The occurrence and cause of carotidynia are unknown.

We describe the case of a 74-year-old woman with diabetes mellitus, hyperlipidemia, and hypothyroidism who developed carotidynia. She consulted us complaining of acute pain and swelling at the left side of her neck and stiffness from the left side of her neck to shoulder in October 2007. She had appeared a few days earlier without any previous infectious symptoms or trauma. The physical findings showed tenderness on palpation from her left carotid bifurcation to internal carotid artery, which was swollen about 2 cm. Her body temperature was 36.3°C. The presence of a carotid bruit was clear. Laboratory findings showed normal peripheral blood cell counts. High-sensitivity C-reactive protein (hs-CRP) was slightly elevated at 0.367 mg/dl (0.046 mg/dl at 6 mos previously) and serum amyloid A protein (SAA) was slightly elevated at 10.5 µg/ml (normal range is less than 8.0 µg/ml). Hepatitis B surface-antigen and hepatitis C virus-antibody tests were negative. ELISA for myeloperoxidase-antineutrophil cytoplasmic antibodies (ANCA) and PR3-ANCA were negative. Ultrasonography (US) of the carotid artery showed a hypoechoic wall thickening of the proximal left internal carotid artery (Figure 1A). Wall thickening was found in 2 different layers of the vessel wall with slight narrowing of the affected vessel. Magnetic resonance imaging (MRI) of the carotid artery showed the following findings: (1) mildly increased intensity in internal carotid sheath was seen on T2-weighted images, (2) fat-suppressed T2-weighted MRI and gadolinium-enhanced T1-weighted MRI showed homogeneous enhancement of the left internal carotid wall including soft tissue around arterial wall (Figures 2A, B), and (3) MR angiogram showed no significant carotid lumen stenosis (image not shown). According to the criteria for carotidynia as defined by the International Headache Society (IHS) classification of 1988, we diagnosed her condition as carotidynia. She was treated with a nonsteroidal antiinflammatory agent for 2 weeks. Her neck pain gradually diminished and was resolved 2 weeks after the onset. Four weeks later, her ultrasonography test showed significantly fewer abnormal findings (Figure 1B). Further, the levels of hs-CRP and SAA were also reduced to 0.020 mg/dl and 2.5 µg/ml, respectively.

Carotidynia indicates not only unilateral neck pain but also various symptoms including headache, sore throat, jaw claudication, dysphagia, malaise, nasal congestion, and lacrimation. We should consider the following diseases and syndromes as differential diagnoses: arterial dissection, cervical disk disease, cluster headaches, myofascial pain syndrome, giant

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**Figure 1.** Ultrasonography of a longitudinal section of the proximal left internal carotid artery. A. Before treatment. Hypoechoic wall thickening of the proximal left internal carotid artery. B. Followup 4 wks later, showing fewer pathological findings.

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cell arteritis, acute pharyngitis, peritonsillar abscess, acute sinusitis, thyroïditis, sialolithiasis, mononucleosis, and cervical adenitis. In our case, these diseases were ruled out.

On the other hand, the second International Headache Society classification in 2004 no longer refers to carotidynia as an independent pathological entity. That is, they concluded that carotidynia was a not validated entity, but a syndrome of a unilateral neck pain.

Currently, the view prevails that the conventional concept of carotidynia as having no structural abnormality should be removed from the previous classification system. These findings of carotidynia on US, computerized tomography (CT), and MRI examinations have recently been reported. In our case, the findings on US and MRI were compatible with the findings of previous reports.

The positive inflammatory findings have not been previously described in carotidynia. However, nonspecific vascular inflammation has been demonstrated histologically in carotidynia and both hs-CRP and SAA levels were slightly elevated in the far-advanced stage of carotidynia in our case, indicating the existence of acute inflammation. Indeed, the measurement of hs-CRP is beginning to be considered as a trivial inflammatory marker of arteriosclerosis, and relative risk of cardiovascular event is associated with increase of hs-CRP. That is, hs-CRP > 0.2 mg/dl is a high risk factor of cardiovascular event. Our most important finding was that the changes of symptoms and images and those of inflammatory findings of hs-CRP and SAA were parallel. Recently, a new disorder concept of “idiopathic carotiditis” was reported. These authors proposed new criteria and our case fulfilled their criteria.

Considering the above, our findings support the hypothesis that carotidynia could be a distinct disease entity, caused by inflammation. In other words, this means that carotidynia may be a subset of vasculitis. We emphasize the importance of measuring hs-CRP and SAA as characteristics of disease activity in patients with carotidynia.

Carotidynia is an age-old disease entity and may be more prevalent than previously thought. We must investigate further cases of carotidynia in order to elucidate its pathophysiology and mechanisms of development, and the association between carotidynia and vasculitis.

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