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## Clinical challenges

# What's in a name?



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### 1. Case report

A 51-year-old man underwent bronchoscopy at an outside hospital for evaluation of cough and pulmonary fibrosis. His medical history was significant for stable rheumatoid arthritis (RA) diagnosed 2 years prior and type 2 diabetes. He had no history of extra-articular RA. His medications were celecoxib, sulfasalazine, metformin, glimepiride, and pantoprazole. He had a history of alcohol abuse and was a previous smoker with a 25 pack-year history. He denied other drug use.

Bronchoscopy under monitored anesthesia care revealed that the arytenoids were mildly erythematous, but was otherwise unremarkable. In the recovery room he became agitated requiring propofol and fentanyl. He was then admitted for observation. Overnight, he had a fever of 103°F (39.44°C) and became tachypneic with irregular breathing and required intubation.

His serum white cell count was variably elevated from 8 to 15 billion cells/L (3.5–10.5 billion cells/L). Arterial blood gases were normal. Initial chest X ray showed chronic changes of pulmonary fibrosis with no evidence of pneumothorax or pneumonia. Computed tomography of the brain was normal. He was treated empirically for meningitis with ceftriaxone 2 g intravenous (IV) every 12 hours, vancomycin 1 g IV every 12 hours, and ampicillin 2 g IV every 4 hours and for seizures with phenytoin. He was extubated the following day and had worsening mental status changes and progressive weakness. He was then transferred to our hospital.

He was alert, but oriented only to person and place. He had mild dysarthria with “mumbling” speech and intact repetition. His pupils were equally round and reactive to light. Facial sensation was intact to light touch, and facial movements were symmetric. On motor examination, his right upper extremity

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was 4/5 proximally and 4/5 distally compared with left upper extremity strength 4–5 proximally and 4/5 distally. In the lower extremities, strength on the right was 4+/5 proximally, 4+/5 distally versus 4–5 proximally and 4/5 distally on the left. Sensation was intact to light touch in all 4 extremities individually, but he had extinction on the left with double simultaneous stimulation. He had difficulty with finger-to-nose testing. He was also noted to have a rash on his ankles bilaterally.

His neuro-ophthalmology examination showed visual acuity of 20/25 in each eye. The pupils were equal, round, and reactive to light with no relative afferent pupillary defect. Intraocular pressure measurements were 10 mm Hg in both eyes. Humphrey visual field testing 24-2 showed a left incomplete incongruous macular splitting homonymous hemianopsia (Fig. 1). Ocular motility was full. External examination, slit-lamp biomicroscopy, and dilated ophthalmoscopic examinations were normal.

What is the differential diagnosis?

What testing should be performed at this time?

## 2. Comments

### 2.1. Comments by Steven A. Newman, MD

Although a computed tomography scan had been normal, the obvious next step would be to obtain a magnetic resonance

imaging (MRI) scan. This would be far more sensitive than computed tomography to recent infarct (diffusion weighted imaging) or abnormalities in white matter tracts (fluid-attenuated inversion recovery) and certainly should be used if microvascular disease is expected. The findings on MRI will likely direct additional testing depending on whether this looks like a local problem or a secondary problem from thromboembolism or systemic pathology.

One other test that might be helpful here would be angiography. This can often give clues to a primary vasculitis, not seen on other forms of imaging study (computed tomography, MRI, etc.). When ordering these tests, it would be important to have a neurologist on board and discuss the potential value of angiography with neuroradiology. More recent studies point out that biopsy and angiography remain the gold standard for diagnosis of small to medium size vessel vasculitis.<sup>22</sup>

## 3. Case report (continued)

MRI of the brain showed multiple areas of diffusion restriction in both cerebral hemispheres, but to a greater extent on the right, including the right frontal, right parietal, and right occipitotemporal gyri consistent with middle cerebral artery territory infarction with relative sparing of the white matter (Fig. 2). Electroencephalography showed lateralized discharges

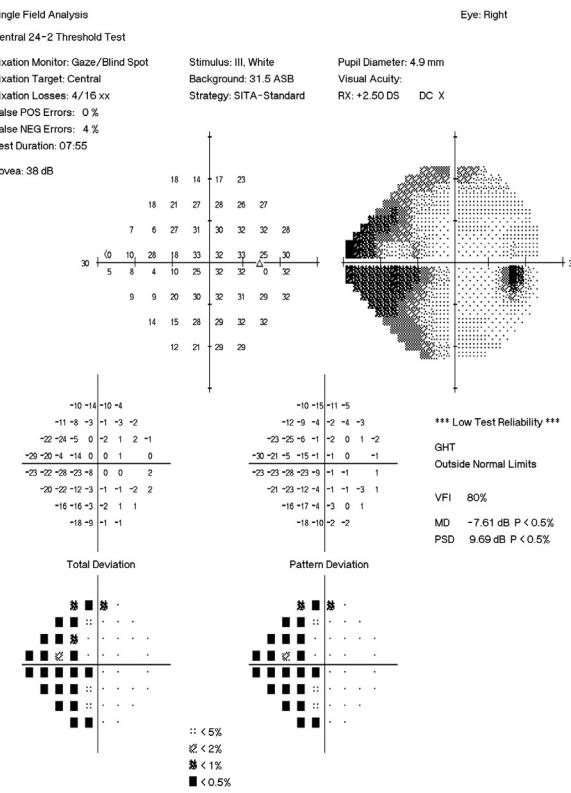
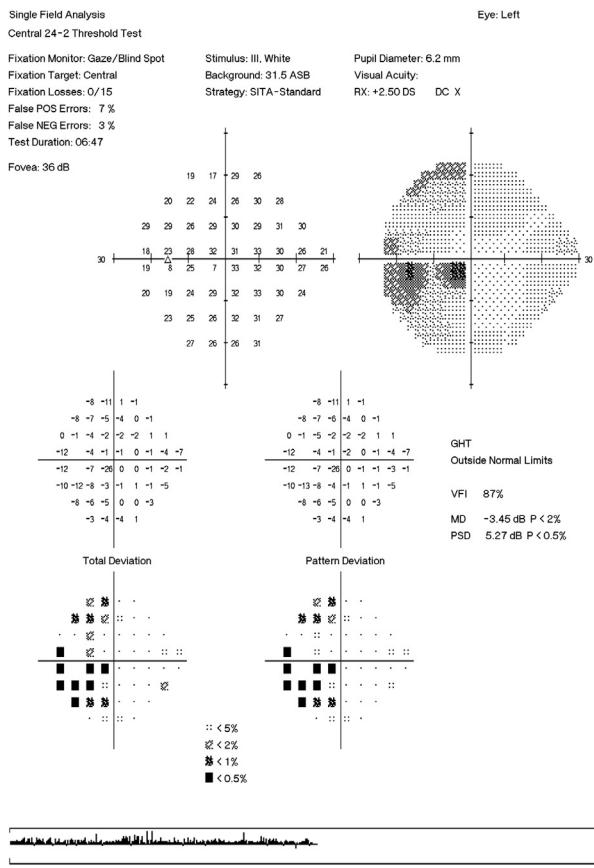
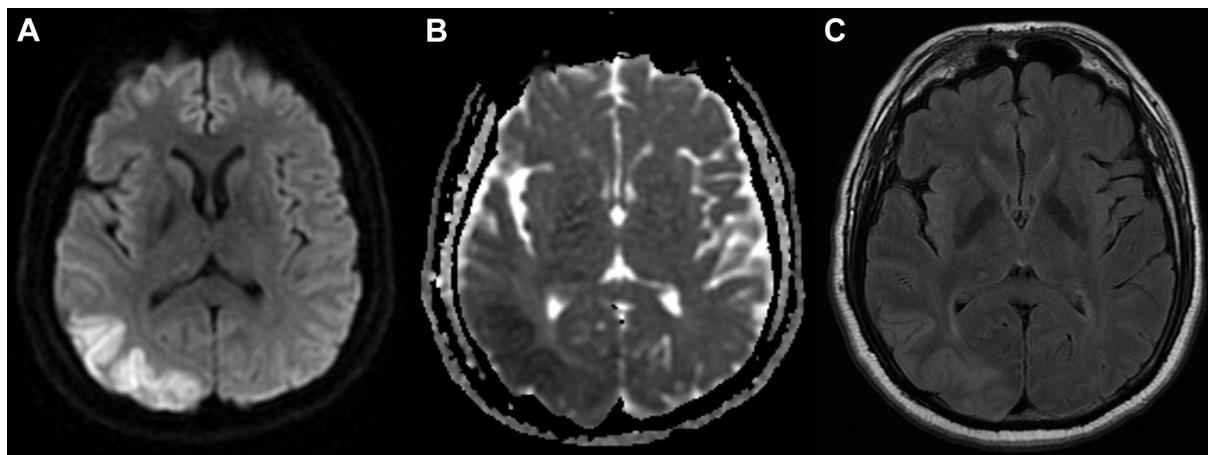


Fig. 1 – Humphrey visual field 24-2. Left incomplete incongruous macular splitting homonymous hemianopsia at initial presentation.



**Fig. 2 – Brain magnetic resonance images. A: Diffusion weighted imaging and B: apparent diffusion coefficient (ADC) axial images show diffusion restriction consistent with ischemic infarction of the posterior right middle cerebral artery territory corresponding with hyperintensity of the C: fluid-attenuated inversion recovery image.**

over the right hemisphere and diffuse slowing. An echocardiogram was normal. Carotid Doppler studies did not show any evidence of hemodynamically significant stenosis. Magnetic resonance angiography of the head showed no evidence of stenosis, and magnetic resonance angiogram of the neck showed no vascular stenosis, occlusion, or vascular malformations. Lumbar puncture showed 9 red blood cells per  $\mu\text{L}$  and 5 white blood cells per  $\mu\text{L}$ , protein of 165 mg/dL (normal, 40–80 mg/dL), and glucose of 153 mg/dL (15–60 mg/dL). There were no oligoclonal bands present. Serum C-reactive protein was 6.91 mg/dL (normal, 0–1 mg/dL), and the erythrocyte sedimentation rate was 39 mm/hour (normal, 0–10 mm/hour). Rheumatoid factor was 42 IU/mL (normal, 0–13 IU/mL). Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) were elevated at 1:1280 (normal <20), and myeloperoxidase level was >30 (normal <20). Antinuclear antibody, cytoplasmic-ANCA (c-ANCA), Sjögren syndrome A antibody, and Sjögren syndrome B antibody levels were all normal.

What further evaluation is indicated?

What treatment should be initiated at this point?

#### 4. Comments (continued)

##### 4.1. Comments by Dr. Newman

That the MRI showed diffusion restriction involving both cortical hemispheres right greater than left immediately alerts us to a multifocal process. This still could be local, but raises the suspicion for a proximal source of embolization or a systemic process. In summary we have a patient with a previous history of RA, diabetes, and alcohol abuse who now has evidence of bilateral peripheral cortical infarcts. In this setting, we are faced with discussing the etiology of his infarcts and possible diagnosis and, most importantly, measures to be taken to prevent progression or recurrence.

The sedimentation rate was mild to moderately elevated at 39 mm/hour, and C-reactive protein was substantially elevated at 6.91 (normal, 0–0.1). Rheumatoid factor was

elevated (not surprising in a patient with known RA). The first question to be answered here is whether this represents a local condition (small vessel peripheral vasculitis), thromboembolic phenomena, or even potentially vasospasm. In these days of multidisciplinary approach to medical problems, it is important to recognize that the inclusion of a neurovascular neurologist would be essential to help analyze the relative risks and suggest additional work-up. If the patient had had a previous history of migraine, something like cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy would be part of the differential diagnosis. As this occurred in the setting of anesthesia, we must immediately include the possibility of unrecognized hypotension, anemia, and for that matter thrombocytosis associated with the procedure itself.

In considering thromboembolic phenomena, one would expect a source in the carotid artery, although the fact that there is bilateral involvement would require bilateral embolization, a much less common occurrence. Bilateral embolization could happen in the setting of a proximal large vessel etiology or even more likely in the setting of a cardiac abnormality (cardiac myxoma, etc.) although this is quite uncommon. If a cardiac source were suspected, it can usually be confirmed on transesophageal echocardiography.<sup>35</sup>

Obviously, one concern here in a patient with a known history of RA would be the possibility of a vasculitis, although central nervous system (CNS) vasculitis associated with RA is actually quite rare.<sup>12</sup> Skin vasculitis in RA is not uncommon and usually involves overlying cutaneous and intra cutaneous rheumatoid nodules. This is interesting because other forms of vasculitis, including CNS involvement, are often unassociated with active synovitis. Other rare causes of vasculitis include those that are drug induced. These have been associated with antibiotics (minocycline and ciprofloxacin), anti-seizure medications such as phenytoin sodium, medications for gout such as allopurinol, and blood pressure medication such as hydralazine, and thyroid medications such as propylthiouracil. In this case we have no medications that would be a likely cause of vasculitis.<sup>13</sup>

If there is evidence or a strong suggestion of a vasculitis, it certainly would not be unreasonable to consider empiric corticosteroid therapy. Before starting steroids it would be important to rule out those factors that could potentially put a patient at risk for significant steroid complications, including a fungal or tuberculosis infection or an active peptic ulcer. In addition to these, relative contraindications for the use of high dose, long-term steroids include diabetes, as diabetics are much more likely to have complications and problems with glucose management.

Assuming the patient had no evidence of a cardiac source for thromboembolic phenomena, especially if the angiogram confirms the presence of vasculitis, an inflammatory basis can be assumed. In the setting of any inflammatory condition, the critical decision is whether or not there is a specific infectious agent. The most common causes of infectious vasculitis include hepatitis (particularly hepatitis B and C) and HIV. Hepatitis C infection is often associated with cryoglobulinemia.<sup>13</sup>

Standard treatment has usually been moderate to high-dose oral steroids. More recently several disease processes have been treated with parenteral IV steroids that actually offer the advantage of higher dose with a relatively lower side effect profile. In spite of the use of steroids, because of the infrequency of these cases, there is no level I evidence, and for that matter precious little anecdotal evidence, for their use.

In the setting of presumed CNS vasculitis, it would be important to look for other sites that might be involved. This would include looking for vasculitis (small and medium vessels) affecting the kidneys and the retina. Other specific forms of vasculitis, particularly polyarteritis nodosa, have a propensity to involve the liver and can best be diagnosed by angiography.

## 5. Case report (continued)

The patient was started on empiric methylprednisolone 500 mg IV twice a day. He was also treated with folic acid and thiamine because of his history of alcohol abuse. He remained afebrile. Blood, urine, sputum, and cerebrospinal fluid serology, stains, and cultures were negative for any infectious organism including West Nile virus, hepatitis B virus, St. Louis virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, human immunodeficiency virus, *Haemophilus influenza*, *Neisseria meningitidis*, group B Streptococcus, *Streptococcus pneumoniae*, acid fast bacilli, and syphilis. Repeat brain MRI was performed showing less diffusion restriction consistent with subacute areas of infarction with no definite new areas of infarction or abnormality elsewhere. The bronchial biopsy was normal. Skin biopsy of the rash on his legs was consistent with leukocytoclastic vasculitis. No infectious etiology was found, and antibiotics were subsequently discontinued. IV methylprednisolone was followed by oral prednisone. The patient was discharged to a rehabilitation facility.

What treatment should be continued at this point?

## 6. Comments (continued)

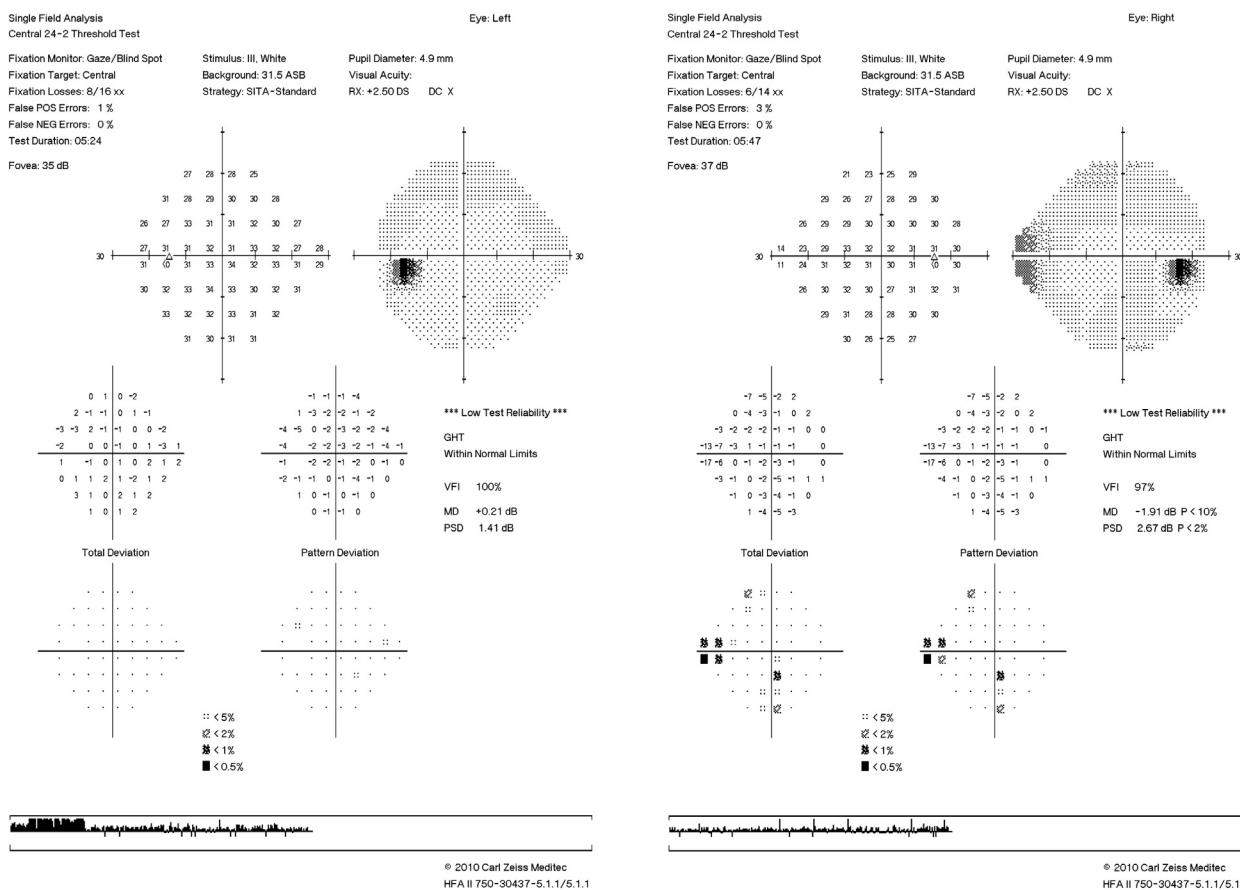
### 6.1. Comments by Dr. Newman

RA-associated vasculitis affecting the CNS is uncommon.<sup>12</sup> A relatively more frequent presentation relates to the effect of RA on the ligaments at the skull base. Pannus involving the clivus and the ligaments of the first 2 cervical vertebrae can result in osseous compression of the brainstem and may be associated with compromise of the vertebral circulation. Inflammatory conditions of the surface of the brain (meningitis<sup>2</sup>) are also uncommon and usually associated with seropositive disease. These changes can best be detected on MRI. Superficial inflammation may result in cranial nerve palsies, hemiparesis, or seizure disorder. With inflammatory involvement of the dura, the spinal fluid is often abnormal, with lymphocytic pleocytosis and elevated protein. The presence of rheumatoid factor in the CSF may be helpful. In view of the unusual presentation and the rarity of rheumatoid CNS vasculitis it is critical to continue to monitor this patient for other signs or symptoms that might suggest alternative pathology.

In view of the known (and common) side effects of long term moderate to high-dose steroids, patients with vasculitis have been treated with various steroid-sparing agents. Medications which have been tried in CNS vasculitis include cyclophosphamide, methotrexate, azathioprine, and tumor necrosis factor (TNF)- $\alpha$  antagonists.<sup>2</sup> Because of the rarity of this condition, there is no level I (and realistically no good level II) evidence for their use. More recently biologic agents (include adalimumab and rituximab [B-cell depilator]) have been employed. It should be kept in mind that these agents are not only expensive, but also have potential side effects. In view of the sparse data and the extremely limited experience with these agents, it is imperative that cases like this be followed extremely closely, constantly monitoring the risk-benefit ratio of any treatment regimen. In this setting, we are prone to become “prisoners of our last case.” This potential for over generalization based on limited experience was probably best stated by Kalman Post, former chairman of neurosurgery at Mt. Sinai, who stated: “the plural of anecdote is anecdotes, not data.”

## 7. Case report (concluded)

After discharge, the patient was maintained on a tapering dose of oral prednisone starting at 0.5 mg/kg. He had clinical improvement of his neurologic symptoms, but relapse of skin vasculitis, as prednisone was tapered. Repeat brain MRI at 8 months after his hospitalization showed fluid-attenuated inversion recovery hyperintensity in the right middle cerebral artery and watershed territories as well as the left frontal parietal vertex. Left posterior temporal and occipital hemosiderin were seen, most likely representing subacute hemorrhage. Lumbar puncture showed 0 red blood cells per  $\mu$ L and 6 white blood cells per  $\mu$ L with protein of 55 mg/dL (normal, 40–80 mg/dL) and glucose of 70 mg/dL (15–60 mg/dL). There were also elevated IgG indices and elevated Q albumin suggesting slight disruption of the blood-brain barrier. He was



**Fig. 3 – Humphrey visual field t 24-2. Resolution of left incomplete incongruous macular splitting homonymous hemianopsia after treatment.**

subsequently treated with IV methylprednisolone for 5 days, and methotrexate was added to his immunosuppressive regimen.

On return for follow up in neuro-ophthalmology clinic, the patient had dramatic improvement in his left homonymous hemianopsia (Fig. 3), along with improvement in the left-sided hemiparesis with continued outpatient rehabilitation.

## 8. Discussion

RA is a chronic progressive systemic inflammatory disorder affecting approximately 1% of the world's population. Joints are the primary target<sup>7</sup>; however, sites of extra-articular manifestations may include the skin, eye, heart, lungs, and blood vessels.<sup>36</sup> Typical neurologic findings in RA include peripheral neuropathy and compressive myelopathy from atlantoaxial dislocation but could also result from rheumatoid nodules, hyperviscosity syndrome, or meningeal vasculitis.<sup>4,23</sup>

RA-related vasculitis (RAV) generally affects small and, more commonly, medium-sized vessels with predilection for the skin and peripheral nervous system.<sup>26</sup> Cerebral RAV is rare, however, occurring in from 1%–8% of patients with RA.<sup>32</sup> RAV is characterized microscopically by lymphocytic infiltration and fibrinoid deposition and necrosis of all vessel wall layers.<sup>24</sup> The clinical presentations of RAV are highly

variable, depending entirely on the vessels and territories involved. These findings range from focal neurologic deficits such as hemiplegia, cranial nerve palsies, or visual field loss to diffuse manifestations such as altered consciousness, confusion, and cognitive impairment or dementia.<sup>4</sup> RAV is also associated with up to a 40% 5-year mortality rate.<sup>5</sup>

Scott and colleagues proposed diagnostic criteria for systemic RAV including patient should fulfill the American Rheumatism Association (ARA) criteria for definite or classical RA with clinical presence of deep cutaneous ulcers, peripheral gangrene, acute peripheral neuropathy or mononeuritis, or severe systemic disease occurring in the presence of typical digital or nail bed infarcts.<sup>21</sup> The 1957 ARA criteria for definite RA required at least 5 criteria and at least 6 weeks of joint symptoms, whereas classical RA consisted of patients who fulfilled 7 of the original 11 criteria.<sup>20</sup> Criteria included morning stiffness, pain on motion, or tenderness in at least 1 joint, swelling in at least 1 joint, swelling of at least 1 other joint, symmetrical joint swelling of the same joint on both sides of the body, subcutaneous nodules, characteristic radiographic evidence, positive sheep cell agglutination, poor mucin precipitate from synovial fluid, and characteristic histologic evidence in synovial membranes or in nodules.<sup>20</sup> The diagnosis of systemic RAV can be confirmed histologically by biopsy of rashes, kidney, or lung or by angiographic evidence of peripheral vascular disease in keeping with a

small vessel arteritis. In our patient, the diagnosis of RAV was fulfilled, given he had ARA definite RA, clinical and radiographic evidence for vasculitis-related cerebral infarcts, and biopsy confirmation of cutaneous vasculitis.

Interestingly, RAV is more common in men and patients with longstanding disease. Improved treatments for RA over the past several years have reduced the risk of RAV. RAV is associated with erosive, seropositive RA and is more frequent with antibodies to cyclic citrullinated peptides, circulating immune complexes, expansion of cytotoxic CD28<sup>null</sup> T cells, and circulating proinflammatory cytokines. Predictors of RAV might include several clinical and genetic factors (Table 1).<sup>25,27–29,33,34</sup> Smoking is also a risk factor for both RA and RAV.<sup>9,13</sup> Smokers with RA are also more likely to have rheumatoid nodules early during the disease, and RA nodules may predict RAV.<sup>11,27,31</sup> Our patient had a 25 pack-year smoking history. There may also be a genetic predisposition toward developing RAV (e.g., HLA-DRB1, double dose of RA-associated HLA-DRB1\*04 alleles, HLA-C\*03, and killer immunoglobulin-like receptors on CD28<sup>null</sup> T cells).<sup>8,15,28</sup>

Another relevant laboratory finding in our patient was the presence of p-ANCA. ANCA positivity is found to be more frequent in secondary CNS vasculitis than in primary CNS vasculitis.<sup>30</sup> P-ANCA antibodies were found in 29% of patients with cerebral vasculitis, suggesting that p-ANCA seropositivity might have a pathogenic role.<sup>16</sup> Some drugs, however, such as hydralazine and propylthiouracil, can cause vasculitis associated with ANCA, with almost all cases involving antibodies to myeloperoxidase rather than to proteinase.<sup>14</sup> Patients with RAV may be antinuclear antibody or p-ANCA positive, but a positive c-ANCA should prompt consideration for alternative diagnosis of primary systemic necrotizing vasculitis.

Although there is no consensus as to the appropriate treatment, combination therapy of methylprednisolone, methotrexate, and cyclophosphamide has produced good results.<sup>1,3,9,12,16,18,37</sup> Two open-label studies favored the use of cyclophosphamide and high-dose glucocorticoids in severe RAV.<sup>6,11</sup>

The potential role of anti-TNF agents in the provocation of or paradoxically treatment of RAV remains ill-defined.<sup>17,19</sup> One survey of a community-based RA showed that the

incidence of severe extra-articular manifestations was lower among those treated with TNF inhibitors, and no cases of RAV were observed in 408 person-years after starting anti-TNF therapy.<sup>29</sup> Another retrospective study from France of 9 patients with refractory RAV reported the use of anti-TNF therapy in patients who had already been treated with high-dose corticosteroids and cyclophosphamide (mean cumulative dose of cyclophosphamide of 8.4 g and a mean prednisone dose of 29.6 mg/day).<sup>19</sup> These authors reported that, for 6 months, 6 patients were in remission (complete remission in 5, partial in 1), treatment failed in 1 patient, and 2 patients discontinued anti-TNF treatment because of side effects. The mean prednisone dose could be reduced to 11.2 mg/day. Relapse did occur in 2 patients, and in only one of these 2 could remission be reestablished by reintroduction of the anti-TNF agent.<sup>10,16</sup> Clinicians should be aware of the possibility of neuro-ophthalmic manifestations of RA including RAV-related homonymous hemianopsia.

## 9. Methods of literature search

MEDLINE was the main resource used for literature search, and an extensive search was performed to locate relevant articles. The keywords used included “cerebral vasculitis”, “rheumatoid arthritis”, and “p-ANCA”. Articles cited in the reference lists of other articles were also considered a potential source of references. We included articles from 1981 to 2014 that contributed information regarding rheumatoid arthritis-associated ophthalmologic, neurologic, and vasculitic manifestations. We included case reports only if they contributed new information about characteristics, diagnosis, or treatment of the disease. The review is based mainly on articles published in the past 2 decades, and only English articles were used in this article.

## 10. Disclosures

The authors reported no proprietary or commercial interest in any product mentioned, or concept discussed, in this article.

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**Table 1 – Predictors of vasculitis in patients with rheumatoid arthritis**

Marker	Suggested explanation	References
Rheumatoid nodules	Signs of microvascular extra-articular inflammation	Voskuyl et al, <sup>31</sup> Turesson et al <sup>27</sup>
Smoking	Vascular damage, immunomodulation	Struthers et al, <sup>25</sup> Turesson et al <sup>28</sup>
HLA-DRB1*04/04 double gene dose	Selection and activation of T cells	Weyand et al, <sup>33</sup> Turesson et al <sup>29</sup>
HLA-C*03 allele	Activation of cytotoxic CD28 <sup>null</sup> T cells	Yen et al, <sup>34</sup> Turesson et al <sup>28</sup>
KIR2DS2 allele	Activation of cytotoxic CD28 <sup>null</sup> T cells	Yen et al <sup>34</sup>

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## A B S T R A C T

### Keywords:

p-ANCA antibodies  
rheumatoid arthritis  
cerebral vasculitis  
autoimmune disease  
homonymous hemianopsia

A 51-year-old man with rheumatoid arthritis and diabetes mellitus presented with new onset left-sided hemiparesis, left-sided neglect, and left-sided incongruous, denser inferiorly, homonymous hemianopsia. Magnetic resonance image of the brain showed prominent swelling of the right frontal, parietal, and occipital lobes greater than on the left with significant change in the fluid-attenuated inversion recovery signal in the gray matter. Perinuclear antineutrophil cytoplasmic antibodies titers were elevated, and skin biopsy demonstrating leukocytoclastic vasculitis. He showed marked clinical and radiographic improvement in association with recovery of vascular abnormalities after the initiation of prednisone, pulse therapy with methylprednisolone, and methotrexate. Clinicians should be aware of the possibility of neuro-ophthalmic manifestations of rheumatoid arthritis, including rheumatoid arthritis-related vasculitis causing homonymous hemianopsia.