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CASE REPORT

Rheumatoid Vasculitis Presenting with Incidental Renal Infarcts: Case Report and Literature Review

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Abstract

Rheumatoid vasculitis is a rare and late complication of rheumatoid arthritis, affecting small to medium sized vessels. Inflammation in the vessel wall produces an occlusive vasculopathy with downstream infarction. We present the case of a 70-year-old female with long standing stable RA status post recent COVID-19 vaccination admitted with community acquired Legionnaires disease found to have an incidental renal infarct on chest imaging without a clear etiology. She improved from a respiratory standpoint but then had a fever spike with repeat imaging showing a second renal infarct and CT angiography showing extensive beading with aneurysmal dilation in the bilateral hepatic and renal arteries consistent with vasculitis. Given extensive RA history, there was a high index of suspicion for rheumatoid vasculitis and she was treated with pulse steroids followed by Rituximab with tapering of steroids and clinical recovery. Her presentation is unique given the salient features, extensive multi-vessel disease without localizing symptoms and potential role of Legionella infection or COVID-19 vaccine in immune activation.

Keywords: Rheumatoid vasculitis, Rheumatoid arthritis, Vasculitis

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, characterized by the presence of autoantibodies; rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP).[1] While the articular manifestations are the predominant clinical feature, a constellation of extraarticular manifestations (EAM) can occur across multiple organ systems typically in severe seropositive disease. Rheumatoid vasculitis is a rare EAM affecting small to medium sized vessels. It is associated with significant morbidity and mortality but fortunately its incidence continues to decline.[2] Presentation varies widely depending on the organ system affected. Our case is a patient diagnosed with rheumatoid vasculitis extensively involving the renal and hepatic vessels uncovered during hospitalization for Legionella pneumonia. She had no localizing symptoms; renal and hepatic function was intact, and the only diagnostic clues were the renal infarcts.

2. Case presentation

70-year-old female with longstanding stable seropositive rheumatoid arthritis, hypertension and osteoporosis presented to the Emergency Department (ED) with fever, chills, fatigue, anorexia, dry cough, dyspnea and nausea which started shortly after receiving her COVID vaccine booster. Her heart rate was 107/min, respiratory rate of 16/min, temperature of 37.8 °C (100 ° F) and oxygen saturation of 98% on room air. After an initial metabolic and infectious workup (Table 1) she was found to have Legionella pneumonia and treated with a Levofloxacin course. On initial CT chest imaging, an incidental infarct was noted in the upper lateral aspect of the right kidney (Fig. 1) for which no obvious etiology could be identified. She was not known to have atrial fibrillation, repeat review of images did not find obvious renal artery abnormalities such as dissection or fibromuscular dysplasia to explain the infarct, urinalysis was bland without proteinuria, hematuria or red blood cell casts. There was concern for a septic embolus, but cultures of urine, blood and sputum

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Table 1. Laboratory results on admission.

Labs	Day 1	Day 8	Day 9	Reference
WBC	21.21 × 10^3/μL	16.53 × 10^3/μL		4–11 × 10^3/μ L
Neutrophil Manual %	88%	96%		21–77%
Bands Manual	10.0%	1.0%		3–17%
Lymphocytes Manual	2%	1.0%		2–6%
Hemoglobin	14.1 g/dL	10.6 g/dL		12.5–15 g/dL
Platelet	204 × 10^3/μ L	340 × 10^3/μ L		140–400 × 10^3/μ L
Sodium	129 mEq/L	131 mEq/L		133-145 mEq/L
Potassium	3.7 mEq/L	3.3 mEq/L		3.3–5.1 mEq/L
Chloride	92 mEq/L	94 mEq/L		96-108 mEq/L
Bicarbonate	24.3 mEq/L	30.5 mEq/L		22-29 mEq/L
Anion Gap	12.7	6.5		5–16
BUN	19 mg/dL	5 mg/dL		6–23 mg/dL
Creatinine	0.55 mg/dL	0.52 mg/dL		0.5–1.00 mg/dL
Glucose	143 mg/dL	97 mg/dL		70–115 mg/dL
Phosphate	2.0 mg/dL	2.7 mg/dL		2.6–4.5 mg/dL
Total Bilirubin	0.8 mg/dL	0.7 mg/dL		<1.0 mg/dL
AST	45 IU/L	48 IU/L		4–31 IU/L
ALT	44 IU/L	59 IU/L		4–31 IU/L
ESR	–	87 mm/h	111 mm/h	<20 mm/h
CRP	–	18.22 mg/dL	9.28 mg/dL	<0.05 mg/dL
Lactic acid	1.9 mmol/L	–	–	0.5–1.9 mmol/L
Procalcitonin	2.02 ng/mL	0.33 ng/mL	–	≤0.10 ng/mL

were without growth and no vegetations were seen on Echocardiogram.

Her initial presenting symptoms improved, and she was being planned for discharge when her fever spiked to 38.8 °C with concomitant rising leukocytosis 11 to 16 × 10^3/μ L. Repeat CT imaging showed a new hypodense lesion, this time in the lower pole of the right kidney concerning for abscess or infarct with questionable wall thickening of the renal arteries suspicious for infectious or vasculitis process.

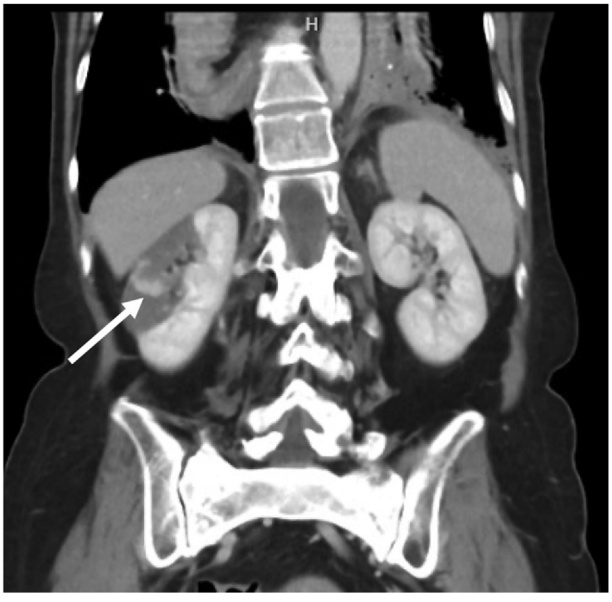

Fig. 1. Arrow points to right renal infarct.

Full dose anticoagulation was initiated, the new renal lesion was too small to be safely sampled by interventional radiology, meanwhile inflammatory markers were now markedly elevated with ESR 87 mm/h (repeat 111 mm/h) and CRP 18 mg/dL. Given the history of RA, rheumatology was consulted to determine if renal infarcts were related to rheumatic disease. RA was diagnosed over 20 years earlier with past flares requiring intermittent steroids, but more recently, disease was well controlled on hydroxychloroquine and methotrexate without any biologic agents. On physical examination, she had bilateral boutonierre's and Z deformity on the hands but no evidence of active synovitis and there were no nail fold infarcts, splinter hemorrhages or Osler nodes. Vasculitis workup (Table 2) included elevated C3 with normal C4 levels, positive RF titer 16 IU/mL with negative anti-CCP. Anti-Nuclear antibody (ANA), Anti-cytoplasmic antibody (ANCA), anti-myeloperoxidase and proteinase were all negative with non-diagnostic anti-phospholipid antibodies. Magnetic resonance angiography (MRA) showed mild stenosis in accessory right renal artery, poorly visualized distal left renal artery suspicious for an obstruction with questionable new infarct in the left kidney. CT angiography revealed aneurysmal dilatation with beading and stenosis in the hepatic arteries, main and accessory renal arteries (Fig. 2) consistent with vasculitis. The possible etiology of her vasculitis included Polyarteritis Nodosa (PAN), infectious vasculitis from legionella infection, COVID-19 vaccine associated vasculitis

Table 2. Autoimmune laboratory results.

		Reference
Complement C3	154 mg/dL	76–100 mg/dL
Complement C4	21.1 mg/dL	15–46 mg/dL
ANA titers	Negative	Negative <1:40 Elevated >1:180
Rheumatoid Factor	16 IU/mL	<14 IU/mL
Cyclic Citrullinated Peptide IgG	<16 units	<20 Units
ANCA screen	Negative	
c-ANCA/anti proteinase 3 Ig	<1.0	<1.0
p-ANCA/myeloperoxidase Ig	<1.0	<1.0
Phosphatidylserine antibody		
IgG	<10 U/mL	<10 U/mL
IgA	<20 U/mL	<20 U/mL
IgM	<25 U/mL	<25 U/mL
Anticardiolipin antibody		
IgM	<2.0	<20.0 APL-U/mL
IgG	<2.0	<20.0 APL-U/mL
IgA	<2.0	<20.0 APL-U/mL
Anti-beta 2 glycoprotein		
IgG	<2.0	<20 SMU
IgA	<2.0	<20 SMU
IgM	<2.0	<20 SMU
Beta 2 Microglobulin	3.24	<2.51 mg/L

and rheumatoid vasculitis. Infectious workup including Hepatitis B screening, cultures of blood, urine and sputum with repeat respiratory pathogen panel was negative. Additionally, autoimmune markers of vasculitis (Table 2) were unremarkable. Because her initial presenting symptoms had abated, oxygen requirement resolved and repeat chest imaging was stable together with her history of severe erosive RA, Rheumatoid vasculitis was deemed the more likely diagnosis. With characteristic vessel findings on CT angiography that was essentially diagnostic, renal artery biopsy was deferred. High dose methylprednisolone 15 mg/kg was started for 3 days then tapered to prednisone 50 mg daily. She was discharged home on a prednisone taper, followed up outpatient with Rheumatology with initiation of Rituximab as a steroid sparing agent. One year after treatment, inflammatory markers had decreased, and she remains symptom free.

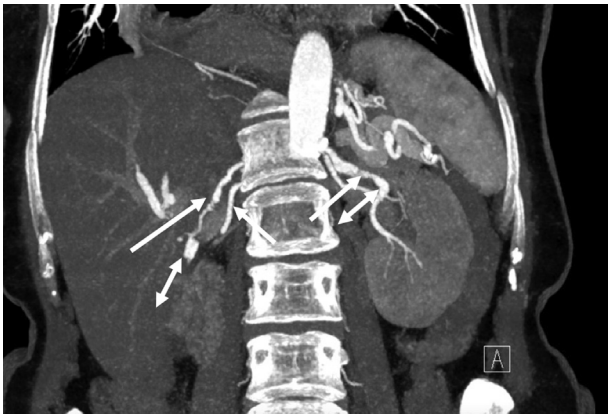

Fig. 2. Arrows showing aneurysmal dilation, stenosis and beading of main and accessory renal arteries.

3. Discussion

Vasculitis occurring in RA was first described over a 100 years ago with inflammatory infiltrate in the vasa nervorum, but it was not until 1954 when Cruickshank succinctly described rheumatoid vasculitis affecting multiple organ systems diagnosed histologically from autopsy.[3,4] Pathogenesis is not completely understood, but the end result of inflammation at the arterial intima is an occlusive vasculopathy causing infarction. Rheumatoid vasculitis is a rare complication of RA occurring in 2–5% of patients and males are 2–4 times more likely to be affected.[5] It typically occurs in advanced RA with a mean onset 10–14 years after RA diagnosis, with presentation occurring when articular disease is quiescent, but deformities have already accrued from past active disease.[2]

In a retrospective case study with one of the largest cohorts of RV patients, Makol et al. identified risk factors of RV including severe rheumatoid arthritis odds ratio (OR 2.02) identified by erosions on imaging, rheumatoid nodule or joint deformity requiring surgery, current smoking (OR 1.58), co-existent peripheral vascular disease (PVD), cerebrovascular disease (CVD) and use of biologics.[6] CVD and PVD imply a high burden of atherosclerosis which is commonly seen in advanced RA while the use of biologics is another reflection of advanced disease.[2] Further risk factors identified include male gender, seropositivity for RF and anti-CCP together with HLA-DRB1 allele.[2,3] Conversely the use of low dose aspirin and hydroxychloroquine has been noted to confer a protective effect.[6] Clinical presentation is heterogenous depending on the organ system affected. The skin and peripheral nervous system are most commonly affected organ systems, followed by eyes and pericardium. Cutaneous manifestations present as non-healing ulcers, nail changes, palpable purpura or ischemic lesions. Peripheral nerve involvement manifests as a sensory or mixed motor and sensory neuropathy.[5] Less common involvement includes episcleritis, scleritis, pericarditis, myocarditis, pulmonary angiitis, mesenteric vasculitis, pachymeningitis or CNS vasculitis. Prominent constitutional symptoms in the form of fever, fatigue, myalgia and weight loss may not be readily noticed especially with significant debility in advanced RA.[7] Where the kidneys

are concerned, RV can affect the glomeruli causing necrotizing glomerulonephritis or less commonly inflammation can be limited to the renal arteries.[8] The latter is associated with decline in renal function unlike our patient who had extensive renal vessel beading and stenosis with normal renal function.

The incidence of RV has been shown to be declining across multiple populations. The Norfolk registry showed a marked decline in the incidence of rheumatoid vasculitis since the 1980s.[3] Bartels et al. in their retrospective cross-sectional study of US veterans spanning 20 years of inpatient and 10 years of outpatient data showed a sustained decline in prevalence of rheumatoid vasculitis that was statistically significant.[9] Myasoedova et al. showed the 10-year cumulative incidence of vasculitis was lower in the 1995–2007 cohort (0.6%) compared to the 1985–1994 cohort (3.6%) in Olmstead county, Minnesota.[10] Ward in his serial cross-sectional study showed a decline in rates of hospitalizations for RV across California from 1983 to 2001.[11] This declining incidence has been attributed to the widespread availability of Disease Modifying Anti-Rheumatic Disease (DMARD) agents including the biologic medications and declining rates of smoking.[12]

While no validated diagnostic criteria are available, the Scott and Bacon criteria has been used and it requires a patient with diagnosed RA to have one or more of the following: (i) deep cutaneous ulcers or extra-articular disease associated with typical nail infarcts or vasculitis on biopsy (ii) peripheral gangrene (iii) peripheral neuropathy or mononeuritis multiplex (iv) biopsy evidence of necrotizing arteritis with systemic illness.[7] Alternative etiologies of vasculitic processes need to be excluded before making definitive diagnosis. It can be particularly difficult to differentiate Polyarteritis Nodosa (PAN) from rheumatoid vasculitis as they both affect small and medium sized blood vessels with similar angiogram patterns and identical biopsy finding of necrotizing vasculitis. The differentiating factors include PAN being strongly associated with HBV infection with skip lesions seen more in PAN. While aneurysms have been reported to occur more frequently in PAN, our patient had widespread aneurysmal dilation spanning across multiple vessels.[13] In cases where histologic tissue is not available such as ours, the final diagnosis usually hinges on history of severe RA. In our patient, biopsy of the renal artery was initially considered but then deferred given characteristic angiographic features.

An additional differential diagnosis we strongly entertained was COVID vaccine vasculitis. Vaccines against SARS-CoV-2 have been pivotal in containing the COVID-19 pandemic. As large segments of the population become vaccinated potential adverse effects including vasculitis have been reported. Vasculitis ranging from cutaneous, large vessel or ANCA associated medium vasculitis have all been described with onset of vasculitis occurring either after the first or second dose of COVID-19 vaccine.[14–17] Furthermore, exacerbations of known underlying vasculitis have been described post vaccination.[18] While COVID-19 vaccine associated vasculitis was considered, this has typically been described in the literature in patients without underlying autoimmune or allergic predisposition.[14,17] Moreover, timing of presentation was consistent with classic rheumatoid vasculitis that presents in advanced RA that has become quiescent. Immune enhancement by her recent COVID-19 vaccine could have triggered rheumatoid vasculitis.

Legionella vasculitis was also considered as a potential differential but ultimately deemed unlikely. Infection with legionella can induce a systemic autoimmune vasculitis that is rare with data limited to case reports. This presents as a pulmonary-renal syndrome that is ANCA positive with patients developing progressive renal failure requiring renal replacement therapy and immunosuppression.[19–21] Classically the pulmonary component shows rapid response to antibiotic treatment while renal failure worsens. All the cases of legionella vasculitis described in literature involved severe lung pneumonia or diffuse alveolar hemorrhage, significant decline in renal function or underlying immunosuppression which our patient all lacked.[19–21]

Laboratory testing can provide supportive data for RV in the form of non-specific signs of inflammation such as elevated ESR, CRP which may be accompanied by low complement levels and hypogammaglobulinemia.[2] Renal involvement may produce proteinuria or active urine sediment on urinalysis which were all absent in our patient. RF and anti-CCP antibodies are typically present and occasionally low titers of ANA and ANCA may be seen. Angiography showing segmental narrowing and dilation is useful when vasculitis affecting the renal arteries, abdominal vessels or aorta is suspected.[8] Microaneurysms are classically considered to be associated with PAN but can very rarely occur in RV as was seen in our patient.[22] The gold standard remains biopsy with histology showing mononuclear cells or neutrophils infiltrating the vessel

wall causing necrosis and disrupting the elastic lamina.[2] While a biopsy should ideally be performed confirmation, diagnosis usually hinges on the clinical picture.[23]

There are no established guidelines for the treatment of RV, treatment deploys aggressive immunosuppression. Combination high dose glucocorticoids and cyclophosphamide have been typically used based on their success in ANCA associated vasculitides. Rituximab is increasingly being used in lieu of cyclophosphamide to avoid its toxicity of ovarian failure, renal failure and increased malignancy.[24] Other regimens used in addition to high dose glucocorticoids include methotrexate, azathioprine and mycophenylate mofetil for mild to moderate cases, rituximab, cyclophosphamide and anti-tumor necrosis factor inhibitors for more severe disease with tocilizumab and abatacept in refractory cases.[6]

Rheumatoid vasculitis is considered to be the most serious extra-articular manifestation of RA with an estimated 40% of patients dying five years into disease onset.[2] Ntatsaki et al. used the Norfolk registry to follow a cohort of 18 patients diagnosed with RV from 2000 to 2010 and found mortality rates at 1 year and 5 year to be 12% and 60% respectively from mostly infection and organ dysfunction.[12] A lower but still substantial mortality rate was seen by Makol with 26% mortality rate at 5-year mark.[6] This mortality has remained unchanged despite declining incidence and advancements in treatment.

4. Conclusion

Rheumatoid vasculitis can present solely with prominent constitutional symptoms and the diagnosis can be obscured by the absence of active articular disease. Diagnosis requires a high index of suspicion, and characteristic angiographic findings can be diagnostic in the right clinical setting.

Conflict of interest

The authors have no potential conflict of interest to declare. The authors received no financial support for the research, authorship, and/or publication of this article.

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