Antineutrophil Cytoplasmic Antibodies associated vasculitis in Patients with Tuberculosis

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Summary

A sixty-five-year-old female was diagnosed disseminated tuberculosis (TB) infection. Two weeks after initiating TB treatment, she developed rapid progressive glomerulonephritis, polyneuropathy, active alveolitis, peripheral ulcerative keratitis (PUK), and episcleritis. Positivity of a high level of anti-Myeloperoxidase (MPO) Antibody, which is compatible with antineutrophil cytoplasmic antibodies-associated vasculitis. After receiving monthly intravenous immunoglobulin (IVIG) treatment and concurrent steroid therapy alongside anti-tuberculosis drugs, her clinical condition improved.

Background

Mycobacterium tuberculosis is a major cause of infection in Thailand resulting in increased mortality and morbidity [1, 2]. In developing countries, TB is widespread. The diagnosis of TB is based on clinical grounds and a large percentage of cases are initiated on specific treatment without bacteriologic confirmation. Small vessel vasculitis shares many features with tuberculosis including constitutional symptoms, hemoptysis, and radiologic findings of lung infiltrates and cavitations[3, 4]. Antineutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against antigens in the cytoplasmic granules of neutrophiles and monocytes, with two major immunofluorescence staining patterns i.e. cytoplasmic (c-ANCA) and perinuclear (p-ANCA). ANCA has been closely related to the diagnosis of a subset of primary systemic vasculitides, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA). ANCA detection has become a major hallmark, particularly, those classifying the cytoplasm of neutrophils in indirect immunofluorescent (IIF) assays (C-ANCA) and targeting proteinase-3 (anti-PR3) in enzyme-linked immunosorbent assay (ELISA) are considered highly specific for GPA. Those antibodies observed in the perinuclear region of neutrophils in indirect immunofluorescent (IIF) assays (P-ANCA) which target myeloperoxidase (anti-MPO) in patients with MPA[5, 6]

Case presentation

A sixty-five-years-old female with bilateral ureteric obstruction and single kidney, essential tremor**,** peripheral arterial disease present with two-months history of fatigue and significant weight loss. Physical examination revealed mild pallor. The blood testing revealed hemoglobin 10.1 g/dL, hematocrit 32.8%, white blood cell count of 15,600 cell/mm^3, and stool occult blood positivity. Her chest radiograph showed multifocal patchy infiltration in both upper lung and right lower lung fields as figure 1A. High resolution computerized tomography (HRCT) of the chest showed multifocal subpleural consolidations and multiple centrilobular nodules (tree in bud) in both lungs as well as bronchial wall thickening at apicoposterior segment of left upper lobe. The sputum collection was positive for TB. A colonoscopy was done. The result revealed hemi-circumferential ulcer with exudate at the terminal ileum. Pathological biopsy of the ileum tissue showed ulcerative changes with granulomatous inflammation and abscess formation, confirming a diagnosis of disseminated TB infection. The patient received anti-tuberculosis medications.

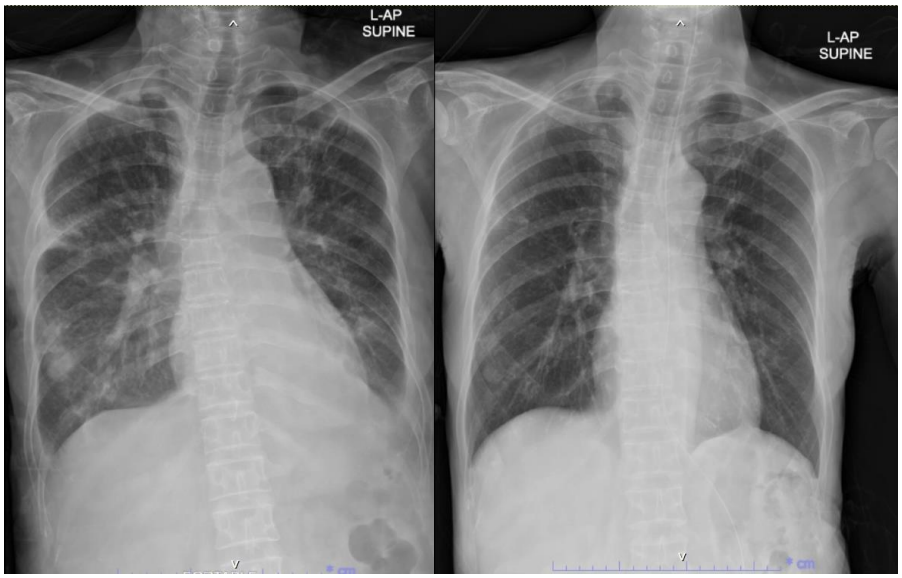
Two weeks after the initiation of TB treatment, her symptoms were deteriorated; poor intake and edema leading to her admitted to the hospital. Upon examination, she had both pretibial pitting edema and decreased pinprick sensation at both feet. She exhibited bilateral conjunctival injection

with normal visual acuity and extraocular eye movements, that an ophthalmologist identified bilateral peripheral ulcerative keratitis (PUK) and bilateral diffuse anterior episcleritis. There were no rashes, lymphadenopathy, active synovitis, or nasal lesion. Her urine showed dysmorphic red blood cells with sub-nephrotic range proteinuria. The complete blood count showed more anemia.

During her hospital stay, her serum creatinine level rose from 1.2 to 3.93 mg/dL. A chest radiograph revealed an increase in patchy infiltration at the right lower lung field compared with previous one. The provisional diagnosis is clinically rapid progressive glomerulonephritis (RPGN). Intravenous dexamethasone and IVIG were prescribed along with the investigations. High dose of steroid was not prescribed because of the recently disseminated TB. A bronchoscopy was done. Lung tissue pathology indicated the presence of interstitial granulomatous inflammation with neutrophilic small vessel vasculitis and capillaritis. Immunofluorescent studies showed a positive result for Immunoglobulin (Ig) G 1+, IgM 1+, and complement 3 2+ in a granular pattern at small vessels and capillaries. The renal biopsy was not performed because she had a single kidney. p-ANCA was found to be positive. With a strongly positive anti-myeloperoxidase antibody. The details of all investigations are shown in table 1.

Diagnosis

A final diagnosis is disseminated TB infection induced ANCA-associated vasculitis (AAV). Because of her vasculitic features followed the TB infection. Her clinical of RPGN, polyneuropathy, PUK, episcleritis, and active alveolitis plus the high positivity of anti-MPO made the diagnose of anti-MPO AAV.



(A) (B)

Figure 1.
(A) Chest X-ray at the diagnosis. Presence of patchy infiltration in both upper lung and right lower lung fields.
(B) Chest X-ray at 6 months after treatment.

Table1. The initial investigations.

Parameter	Result
White cell count	15.18 x 10^9 /L
Neutrophil count	84.1 %
Lymphocyte count	8.6 %
Monocyte count	4.1 %
Eosinophil count	2.8 %
Red cell count	3.33 %
Hemoglobin (Hb)	8.7 g/dL
Hematocrit (HCT)	27.8 %
Mean corpuscular volume (MCV)	83.5 fL
Platelets count	502 x 10^9 /L
Creatinine	2.83 mg/dL
EGFR-EPI	17 ml/min/1.73m^2
Albumin	2.6 g/dL
Alkaline phosphatase	79 (40-150 U/L)
Aspartate transferase	17 (5-34 U/L)
Alanine transferase	19 (0-55 U/L)
C reactive protein	40.75 mg/L (<1 mg/L)
ESR	84 mm/hour
Urine analysis	Protein 2+, positive granular cast and cellular cast
Random urine protein/urine creatinine ratio	3.24 g/g.Cr
Antinuclear antibody	Positive homogeneous pattern, titer 1:80
Complement (C_3)	62 mg% (90-180)
CH50	37.44 U/mL (42-95)
Antineutrophil cytoplasmic antibodies (ANCA) by IFA	Positive of p-ANCA
Anti-MPO (ELISA)	> 200 RU/mL (Ref. <20 RU/mL)
Anti-PR3 (ELSA)	< 2 RU/mL (Ref. <20 RU/mL)
HIV, hepatitis B, hepatitis C	Negative
HRCT	Multifocal subpleural consolidations, and multiple centrilobular nodules (tree in bud) in both lungs and bronchial wall thickening at apicoposterior segment of left upper lung
Pulmonary tissue	Pathology: Presence of interstitial granulomatous inflammation with neutrophilic small vessel vasculitis and capillaritis Negative for AFB, GMS, Fite, PAS Immunofluorescent study: Positive for IgG 1+, IgM 1+, C3 2+ granular pattern at small vessels and capillaries
Ileal tissue	Pathology: Ulcer with granulomatous inflammation and abscess No viral cytopathic effect is seen. Negative for malignancy Special stain: AFB and GMS are negative. PCR for TB: negative
Sputum PCR for TB	*M. tuberculosis* complex positive

ESR: Erythrocyte Sedimentation Rate; Anti-PR3: Anti-Proteinase 3 Antibodies; anti-MPO: Anti-Myeloperoxidase Antibodies; HIV: Human Immunodeficiency Virus; HRCT: High Resolution Computed Tomography; PCR: Polymerase Chain Reaction; TB: Tuberculosis; eGFR-EP estimated Glomerular Filtration Rate; p-ANCA: Perinuclear – ANCA; AFB: acid fast bacilli; GMS; Grocott methenamine silver stain; PAS: Periodic acid-Schiff stain

Treatment and outcome

The monthly IVIG and a moderate dose of prednisolone were prescribed along with antituberculosis medications, followed by Mycophenolate mofetil (MMF). After 6 months and 1 year of treatment, the patient's clinical and serological parameters, as well as chest radiograph were improved (Figure 1(B), Figure 2 and Table 2). Immunosuppression was slowly tapering. Her creatinine settled to a baseline. Anti-tuberculous therapy was continued for a total of 6 months. She has remained in complete remission until the present day, with subsequent anti-MPO testing remaining negative.

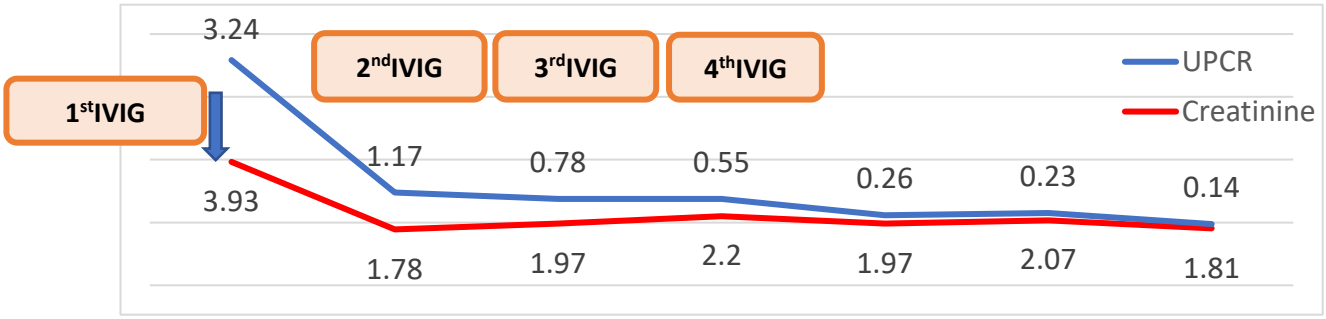


Figure 2 Creatine level and Urine Protein to Creatinine Ratio (UPCR) were monitored during treatment.

Table 2. Improvement of parameters after treatment

	1ST IVIG	2nd IVIG	3rd IVIG	4th IVIG	6mo	12mo	24 mo
Anti-MPO(RU/mL)	>200	120.95	39.17	11.38		6.43	<2
BVAS	27			12	12	4	2
Prednisolone	30mg	20mg	20mg	15mg	7.5mg	5mg	2.5mg
MMF					1000mg	1000mg	500mg

IVIG: intravenous immunoglobulin; BVAS: The Birmingham Vasculitis Activity Score; MMF: Mycophenolate mofetil

Discussion

The distinction between TB and vasculitis can be difficult at disease onset, thereby conferring a potentially elementary differential diagnosis role for ANCA testing[7], hence the association of pulmonary TB with AAV is unusual. Establishing the definitive etiology when these two differential diagnoses are considered is difficult, considering that they share similar clinical, radiological, and histopathological features.

The association between TB and AAV are includes the first, TB which can mimic many conditions of vasculitis[3]and can produce secondary small-vessel vasculitis such as palpable purpura, erythema, urticaria, blisters, ulceration. Firstly, tissue was damaged secondary to deposition of immune complexes, endothelial invasion, the presence of self-reactive B and T lymphocytes, direct injury to the vessel wall, along with hypersensitivity vasculitis[8]. The second, TB involves infectious processes that are associated with the development of ANCA which recognize bactericidal/permeability increasing protein (BPI-ANCA). The latter, it activates neutrophils through the formation of immune complexes with BPI, leading to the formation of neutrophil extracellular traps (NETs), which may play a role in the pathogenesis of vasculitis. The third, the elevation of ANCA in serum is secondary to infectious processes; in TB, this occurs[9, 10] . The prevalence of ANCA in TB has been reported from 10-40%, the majority being p-ANCA. Pradhan et al. reported the presence of ANCA in 30% of TB patients, in which there was also a correlation between p-ANCA (52.4%) and C-ANCA(38.1%) patients with TB, prevailing the anti-MPO pattern (47.6%)[3]. Texeira et al. also found similar data in their survey: up to 6% of TB patients had a p-ANCA pattern and 4% a c-ANCA pattern[11]. The fourth, anti-TB drugs can induce AAV; clinical symptoms usually occur after starting drugs and improve after discontinuation. Isoniazid and rifampicin were reported, but the mechanism was unclear.[12-14]Finally, complication from AAV treatment increases the risk of tuberculosis infection in a patient who is receiving immunosuppression for the management of vasculitis.

Clinically, both TB infection and AAV usually have predominant constitutional symptoms. AAV has some features such as hemoptysis, ocular manifestations (scleritis, uveitis, keratitis), renal manifestation (hematuria, proteinuria, renal impairment) but rare leukocytoclastic vasculitis and pulmonary cavitary lesions on computerized tomography scan, Pathological examination of both can reveal granulomas, but caseating granuloma mostly found in TB infection.

In this case, we herein report a case which AAV with TB co-infection, we suspected that the diagnosis is TB induces AAV due to the development of clinical glomerulonephritis, bilateral PUK, episcleritis, polyneuropathy and active alveolitis after recent TB infection and high level of anti-MPO. Previous knowledge, anti-MPO AAV is no tissue granuloma formation, our hypothesis is the granulomatous pulmonary tissue may be from with her tuberculosis parallels with the active small vessel vasculitis of AAV. Finally, there was a good response to steroid and IVIG with continued anti-TB treatment supports the diagnosis of TB induces AAV.

Conclusion

There are many associations between TB and AAV. Vasculitis shares many features with tuberculosis and should be considered in the differential diagnosis, especially in atypical TB infections such as clinical glomerulonephritis, scleritis, neuropathy. On the other hand, tuberculosis should be considered in AAV patients who experience clinical worsening after AAV treatments. Clinicians should have a high index of suspicion, as the treatment of these conditions differs. Misdiagnosis and treatment delays can lead to life threatening consequences.

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