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Unclassified Vasculitis with Episcleritis, Thrombophlebitis, Deep Vein Thrombosis, Pulmonary Vasculitis, and Intracranial Vasculitis: An Autopsy Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 67
Final Diagnosis: Unclassified vasculitis
Symptoms: Fever • ocular pain • erythema • chest pain • headache
Medication: —
Clinical Procedure: Biopsy
Specialty: Rheumatology

Objective: Rare disease

Background: Systemic vasculitides constitute heterogenous conditions affecting many organs and systems through blood vessel inflammation. Although there are some classifications for vasculitis, several vasculitides are "unclassified" because they cannot be clearly assigned to one of the known entities.

Case Report: We report an autopsy case of a 67-year-old Japanese man who presented with fever, ocular pain, erythema, chest pain, and headache. The disease caused episcleritis, thrombophlebitis, extensive deep vein thrombosis, multiple pulmonary nodules and masses, hypertrophic pachymeningitis, and hyper-intensity areas in brain parenchyma on magnetic resonance images. Histopathology of the pulmonary nodule confirmed vasculitis affecting medium-to-small veins and arteries without necrotizing vasculitis or granulomatous inflammation. We diagnosed the patient with unclassified vasculitis based on the clinicopathological characteristics. Steroids in combination with immunosuppressants were used, but the disease was refractory and relapsing. The disease activity was eventually controlled with rituximab, but the patient died of bronchopneumonia. On autopsy, lung and brain findings indicated healed vascular inflammation.

Conclusions: This is the first case report of unclassified vasculitis, which is characterized as medium-to-small-sized arteritis and phlebitis, causing episcleritis, thrombophlebitis, deep vein thrombosis, pulmonary vasculitis, and intracranial vasculitis. The clinical conditions share some similarities with granulomatosis with polyangiitis and Behçet's disease; however, they meet no classification criteria of any specific vasculitis. More cases need to be analyzed to confirm our findings.

MeSH Keywords: Arthritis • Multiple Pulmonary Nodules • Phlebitis • Relapsing Fever • Vasculitis • Vasculitis, Central Nervous System

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Background

Systemic vasculitides constitute heterogenous conditions affecting many organs and systems through blood vessel inflammation. The etiology and pathogenesis of vasculitides are not completely understood. The Chapel Hill Consensus Conference (CHCC) in 1994 designated definitions for vasculitis, and 10 systemic vasculitides were defined according to clinical and pathological features [1]. The definitions were revised by the CHCC in 2012, and 7 categories and 26 diseases were defined [2]. However, several vasculitides remained "unclassified" because: 1. they were not included in the CHCC definitions (e.g., antiphospholipid antibody syndrome, Buerger disease, and Eale's disease), 2. the relationship between vasculitis and other manifestations remains unclear (e.g., IgG4-related disease and chronic periaortitis), and 3. the vasculitis cannot be clearly assigned to one of the known entities (e.g., vasculitis characterized by acral necrosis or granulomatous giant cell polyphlebitis) [3]. For the third reason, these vasculitides are termed "unclassified vasculitis" or "undifferentiated vasculitis", but their nomenclature is not clearly defined.

We report the first case of unclassified vasculitis, which is characterized as medium-to-small-sized arteritis and phlebitis, causing relapsing fever, episcleritis, thrombophlebitis, deep vein thrombosis (DVT), pulmonary vasculitis, and intracranial vasculitis. We discuss the case with histopathological investigation of the antemortem biopsy and autopsy findings.

Case Report

A 67-year-old Japanese man was admitted to our hospital with fever and severe headache. He had no significant medical or family history. Eight years prior, he was admitted to our hospital with fever, headache, ocular pain, and erythema nodosum-like rash on the extremities. Laboratory data demonstrated marked inflammation [white blood cell count, 9880/μL; C-reactive protein (CRP), 19.5 mg/dL]. The ocular condition was diagnosed as episcleritis (Figure 1A), and skin biopsy of erythema revealed thrombophlebitis (Figure 1B). Hyper-intense areas at the globus pallidus were noted by head magnetic resonance imaging (MRI) on T2-weighted images (T2WI) (Figure 1C). The patient was first suspected to have neuro-Behçet's disease (NBD) because of the intracranial lesion and thrombophlebitis; however, the diagnostic criteria for Behçet's disease (BD) [4,5] were not satisfied because of the lack of oral aphthosis, genital ulcer, and uveitis, and negative pathergy test. The human leukocyte antigen test was positive for A23, A33, B39, B44, DR4, and DR13, which are not risk factors of BD [6]. He was next suspected to have small-vessel vasculitis, such as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis, because of the complication of episcleritis; however, proteinase 3-anti-neutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA were negative, and no other evidence supported these diagnoses. We tentatively diagnosed him with unclassified vasculitis. After initiation of intravenous methylprednisolone (mPSL) pulse therapy (1000 mg/day of mPSL for 3 days) followed by 1 mg/kg/day of prednisolone (PSL), all symptoms and inflammatory markers immediately improved. However, he repeatedly relapsed with fever, headache, episcleritis, and erythema after PSL was tapered to under 15 mg/day. Azathioprine and colchicine were added, but

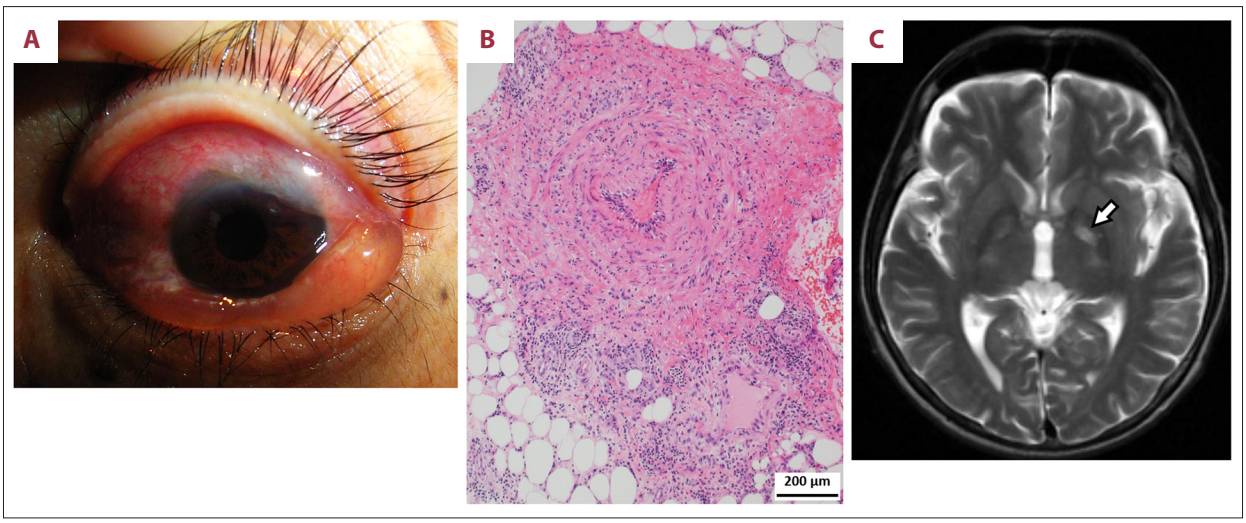

Figure 1. Images taken during the first hospitalization. Diffuse episcleritis with conjunctival edema (**A**). Skin biopsy of the erythema revealed thrombophlebitis in the subcutaneous fat (magnification 100×, hematoxylin and eosin [H&E]) (**B**). Head MRI demonstrated a high-intensity area at the globus pallidus on T2WI (arrow) (**C**).

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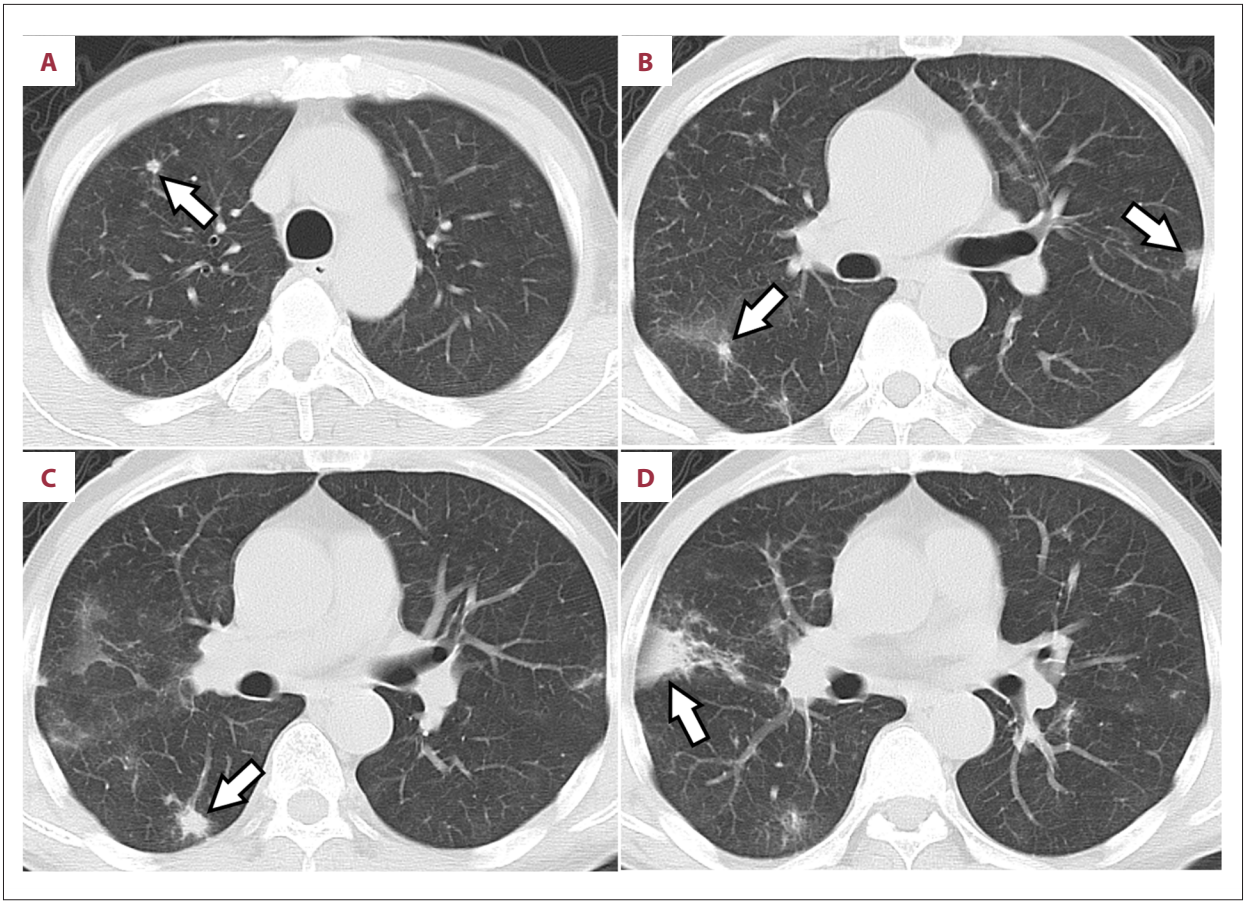

Figure 2. Chest CT revealed multiple nodules and slight infiltration (arrow: **A**, right S1; **B**, right S6 and left S4; **C**, right S6; **D**, right S4).

these did not inhibit palindromic flare. Gene analysis was performed to investigate autoinflammatory disease. Heterozygosity for the E148Q mutation in the *MEFV* gene was found, but it was considered to be a gene polymorphism because the role of E148Q in familial Mediterranean fever (FMF) remains controversial [7,8], and the patient's clinical symptoms and ineffectiveness of colchicine did not meet the criteria for FMF [9]. Tumor necrosis factor receptor superfamily member 1A gene mutation for tumor necrosis factor receptor-associated periodic syndrome [10] was also absent.

Six years prior to the current hospitalization, the patient was readmitted to our hospital because of fever and new-onset chest pain with inflammatory markers. Computed tomography (CT) revealed multiple pulmonary nodules (Figure 2A–2D), and he underwent biopsy of the nodule in the right S6 by video-assisted thoracic surgery. The biopsy specimen exhibited vasculitis in both arteries and veins, which were predominantly infiltrated by lymphocytes and plasmacytes (Figure 3A–3H). The size of the affected vessels was medium-to-small, and capillaritis was not detected. Intra-alveolar fibrosis with infiltration of lymphocytes and plasmacytes was also observed (Figure 3F–3H). Typical pathological manifestations of GPA, such as necrotizing vasculitis and granulomatous lesions [11], were not found. These pathological findings did not meet any existing classification criteria for specific vasculitides. The clinical findings also did not meet the criteria for GPA [12] or any other diagnostic criteria for vasculitis, including the CHCC definitions [1,2]. We decided to treat the unclassified vasculitis with PSL at 1 mg/kg/day in combination with biweekly intravenous cyclophosphamide (IVCY) at 500 mg for 6 courses. The pulmonary nodules and inflammatory markers immediately improved with the combination therapy. However, the patient had repeated relapses of fever, headache, and multiple pulmonary nodules whenever the IVCY course finished. Sufficient doses of methotrexate, cyclosporine, and infliximab were each administered as alternate immunosuppressants for cyclophosphamide, but they were ineffective.

One year prior to the current hospitalization, the patient developed extensive DVT. Thrombosis extended from the inferior vena cava to the left femoral vein with inflammatory markers (CRP, 30.6 mg/dL). Antiphospholipid antibodies were negative, and no other thrombotic predisposition was noted, so we suspected that the DVT was caused by phlebitis associated with his unclassified vasculitis. We restarted biweekly IVCY at 500 mg

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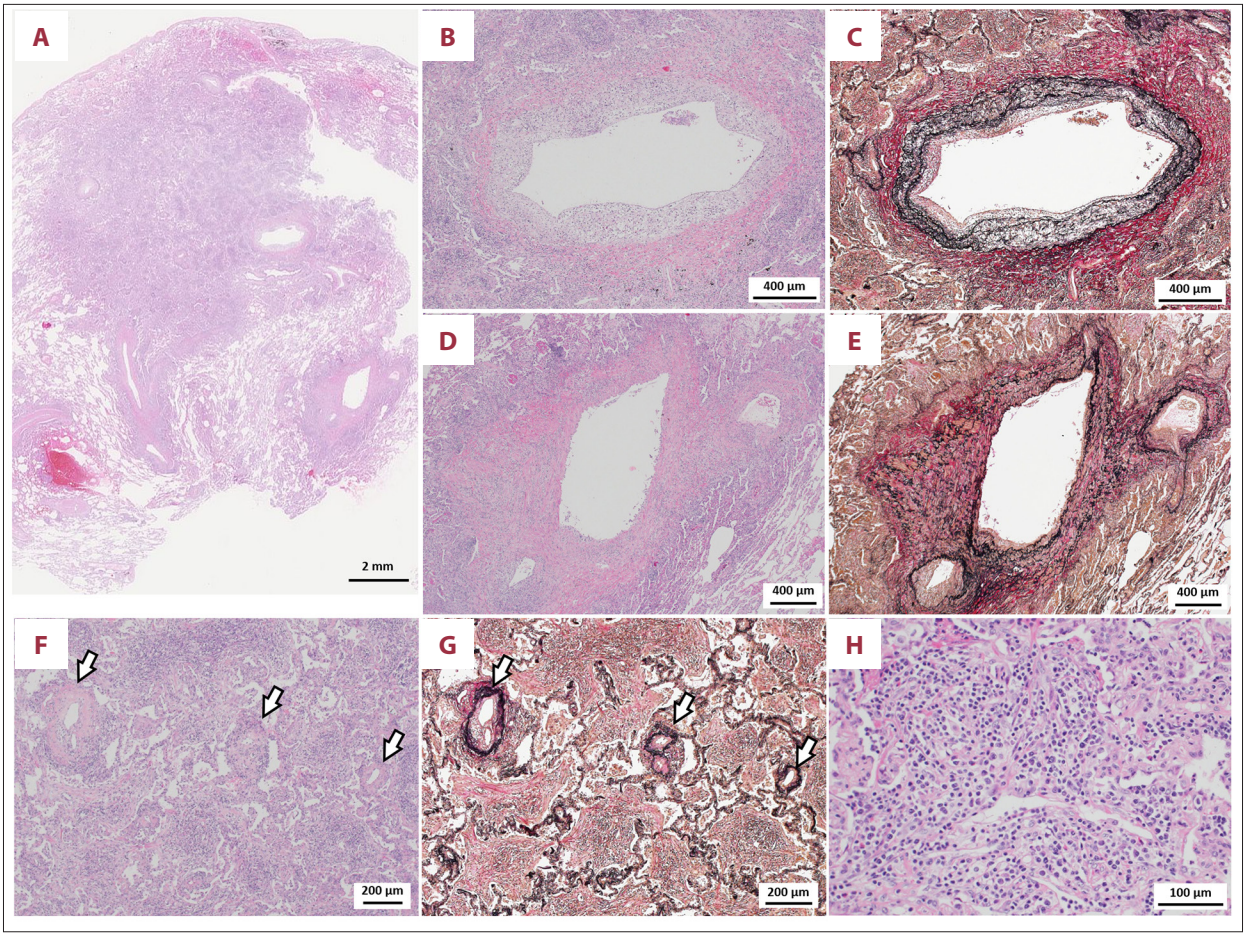

Figure 3. Antemortem histopathological findings of the lungs. Loupe image of the biopsy specimen (**A**). Vasculitis of a middle-sized artery (**B, C**), veins (**D, E**), and small-sized arteries (arrow in **F, G**). Lymphocyte and plasmacytes dominated the inflammatory cells that infiltrated into vessel walls and the perivascular area, and intimal hypertrophy was observed. Intra-alveolar fibrosis with infiltration of lymphocytes and plasmacytes (**F, G, H**). Magnification: **A**, loupe (H&E); **B**, 40× (H&E); **C**, 40× (Elastica van Gieson [EVG]); **D**, 40× (H&E); **E**, 40× (EVG); **F**, 100× (H&E); **G**, 100× (EVG); **H**, 200× (H&E).

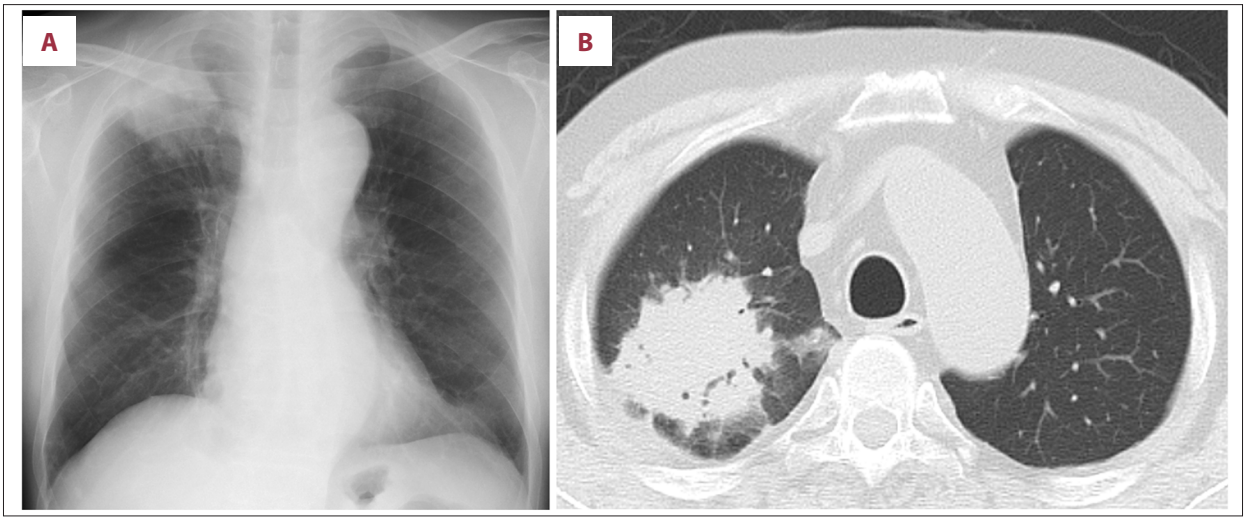

Figure 4. Chest radiography during the final hospitalization demonstrated a mass in the right upper lobe (**A**). Chest CT revealed a pulmonary mass in the right S1 (100×100 mm) (**B**).

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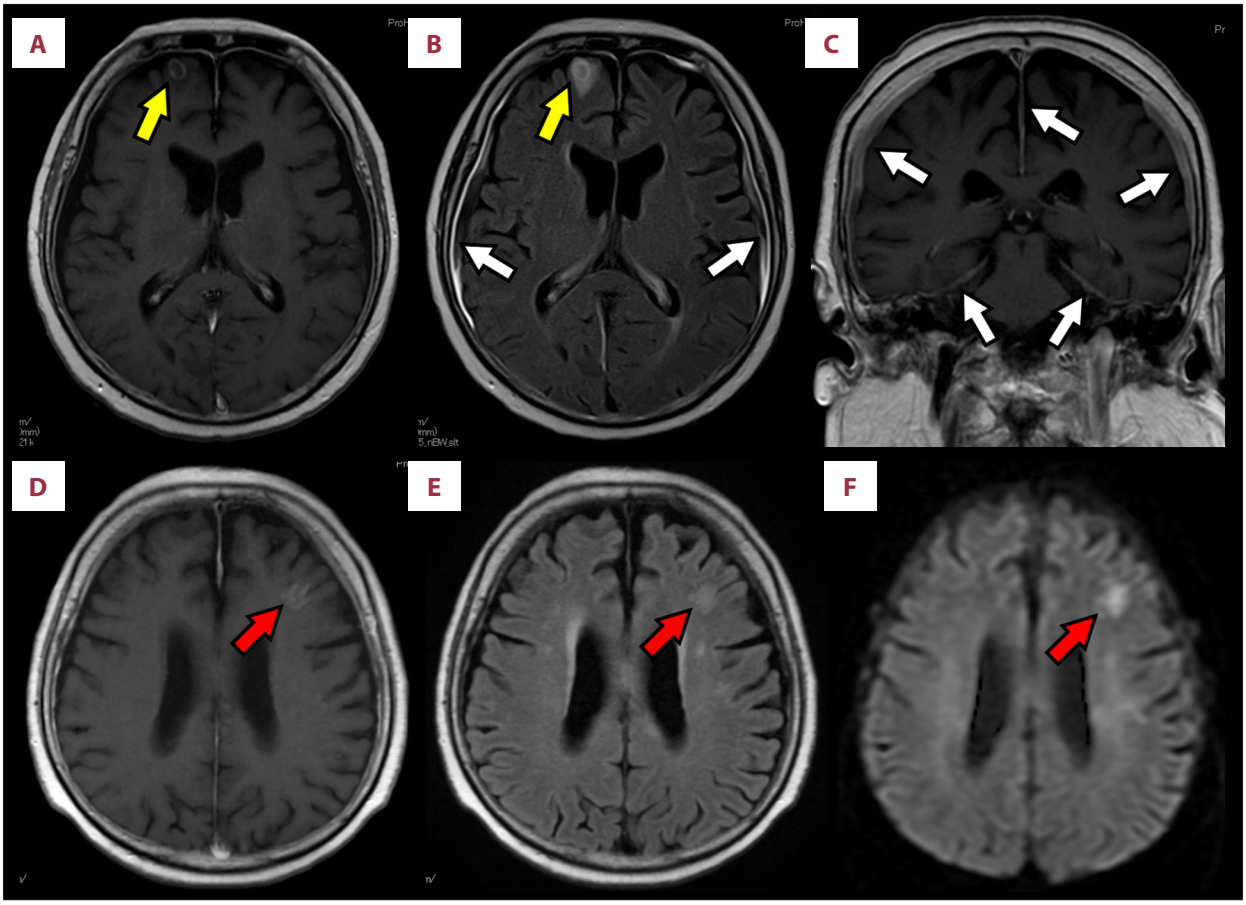

Figure 5. Gadolinium-enhanced MRI revealed a ring-enhancing lesion (yellow arrow) in the frontal lobe (10×7 mm) (**A**; Gad-TIWI, **B**; Gad-FLAIR), hypertrophic pachymeningitis (white arrow) (**B**; Gad-FLAIR, **C**; Gad-TIWI), and multiple patchy hyper-intense areas (red arrow) were observed from the left frontal lobe to the parietal lobe (**D**; Gad-TIWI, **E**; FLAIR, **F**; DWI).

for 6 courses with anticoagulation therapy, and satisfactory responses were observed with these therapies.

Two weeks prior to the current hospitalization, severe headache and chest pain relapsed. Chest radiography and CT revealed a large pulmonary mass in the right S1 (Figure 4A, 4B). The patient was readmitted for further investigation. Laboratory data on admission indicated normocytic normochromic anemia with hemoglobin at 8.9 g/dL and elevated CRP levels at 14.7 mg/dL, and he was negative for rheumatoid factor and antinuclear antibody. Cytoplasmic ANCA and perinuclear ANCA were not detected by immunofluorescence assay. Proteinase 3-ANCA and myeloperoxidase-ANCA were also negative by ELISA. Regarding infection, interferon-gamma release assays and β-D-glucan were negative, and blood and sputum cultures were negative for bacteria, mycobacteria, and fungi. Bronchoscopy with bronchoalveolar lavage and brushing cytology for the right S1were performed, and no microorganism or neoplastic cells were detected. Thus, we suspected that the pulmonary mass was associated with his unclassified vasculitis.

For investigation of severe headache, gadolinium-enhanced brain MRI was performed. Hypertrophic pachymeningitis (HP) and a ring-enhancing lesion with central hyper-intensity on diffusion-weighted images (DWI) were observed (Figure 5A–5C). Two weeks later, MRI revealed multiple patchy hyper-intense areas on T2WI, fluid-attenuated inversion recovery (FLAIR), DWI, and gadolinium-enhanced T1-weighted images (Gad-T1WI) (Figure 5D–5F). Cerebrospinal fluid (CSF) examination demonstrated normal cytology, negative immunoglobulin G (IgG) index (0.48), and high interleukin (IL)-6 levels (14.4 pg/mL), which excluded demyelinating disorders such as multiple sclerosis. The CSF culture was sterile, and no neoplastic cells were detected. We suspected that these intracranial lesions were also caused by the underlying unclassified vasculitis, and PSL at 1.5 mg/kg/day was administered.

Two weeks after receiving PSL at 1.5 mg/kg/day, the patient rapidly developed respiratory failure with fever and elevated CRP levels. Chest CT revealed nodules and masses with slight consolidation at the bilateral S6–10 (Figure 6A, 6B). Bronchoalveolar lavage revealed no evidence of alveolar

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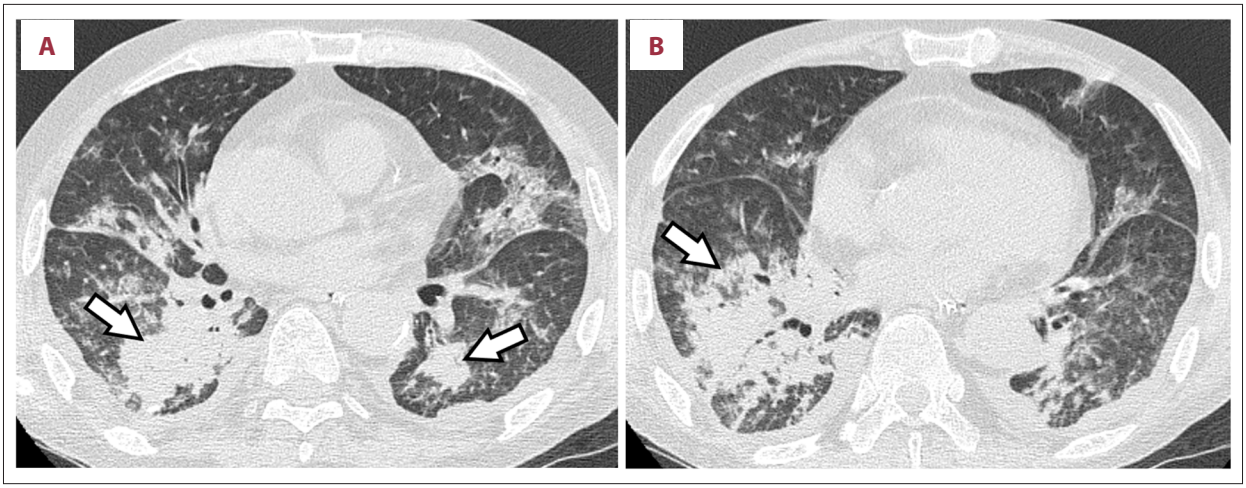

Figure 6. Chest CT revealed nodules and masses with slight consolidation at the bilateral S6–10 (arrow) (**A, B**).

hemorrhage or pneumonia (bacterial, pneumocystis, fungus, and mycobacterium). We suspected that the pulmonary masses were associated with his unclassified vasculitis and administered mPSL pulse. His respiratory condition and the pulmonary mass and nodule immediately improved after the treatment. However, the effects of the mPSL pulse were temporary, and multiple pulmonary nodules and masses with respiratory failure repeatedly relapsed. We initiated rituximab (RTX) at 375 mg/m^2/week as an additional immunosuppressant, which is widely used to treat vasculitides, particularly ANCA-associated vasculitis [13–15]. RTX was immediately effective for his presenting symptoms, including the multiple pulmonary nodules and masses with respiratory failure, headache, and elevated CRP levels. Therefore, RTX was continued and PSL was tapered gradually.

After the third course of RTX, fever and respiratory failure without pulmonary nodules developed. Pneumonia was suspected and antibiotics were administered, but the patient died on the 155th hospital day.

An autopsy was conducted to identify the cause of death and clarify the diagnosis of unclassified vasculitis. Pathological findings of the lungs revealed no vasculitis, but intimal hypertrophy and adventitial fibrosis remained in some parts (Figure 7A–7D). Age-related vasculopathy-like changes were not shown in either normal vessels or in vessels which had intimal hypertrophy and adventitial fibrosis. Bronchopneumonia was the major finding of the lungs, which exhibited neutrophil and macrophage infiltration into the peripheral bronchi and alveolar spaces on culture of the lung tissue (*Enterobacter cloacae*, *Enterobacter faecium*, and *Staphylococcus haemolyticus*). Mycobacteria, nocardia, and fungal infection were negative. The cause of death was suspected to be bronchopneumonia. The intracranial lesion demonstrated hypertrophy of the cerebral dura mater, indicating HP (Figure 7E), and small foci of parenchymal necrosis with gliosis scattered at the gray mater corresponded to the patchy lesions on brain MRI (Figure 7F). Small necrotic lesions were suspected to be healed vascular inflammation rather than cerebral infarction because no microembolisms were found.

The clinicohistopathological findings for the patient's vasculitis were as follows: antemortem biopsy findings of thrombophlebitis and pulmonary vasculitis affecting both veins and arteries of medium-to-small-sized vessels without necrotizing vasculitis or granulomatous inflammation; autopsy findings of intracranial vasculitis (HP and small necrotic foci with gliosis in brain parenchyma); and clinical findings of episcleritis and extensive DVT. Thus, we concluded that the patient had a previously unreported type of unclassified vasculitis.

Discussion

This is the first case report of unclassified vasculitis characterized by medium-to-small-sized arteritis and phlebitis, causing relapsing fever, episcleritis, thrombophlebitis, DVT, pulmonary vasculitis, and intracranial vasculitis. The clinical conditions share some similarities with GPA and BD; however, they were not sufficient to diagnose GPA or BD, nor any specific vasculitis (Table 1). Next, we discuss the 3 initial characteristic points in our case considering the differential diagnosis: 1. presenting pulmonary vasculitis with multiple nodules and masses, 2. presenting intracranial vasculitis with HP and cerebral lesions, and 3. affecting arteries and veins.

First, pulmonary manifestations were an individual finding in our case. GPA was primarily considered as the differential diagnosis because GPA is the most common cause of pulmonary nodules and masses in noninfectious inflammatory conditions. In GPA, up to 90% of radiographic abnormalities seen at presentation are pulmonary nodules and masses [16], and

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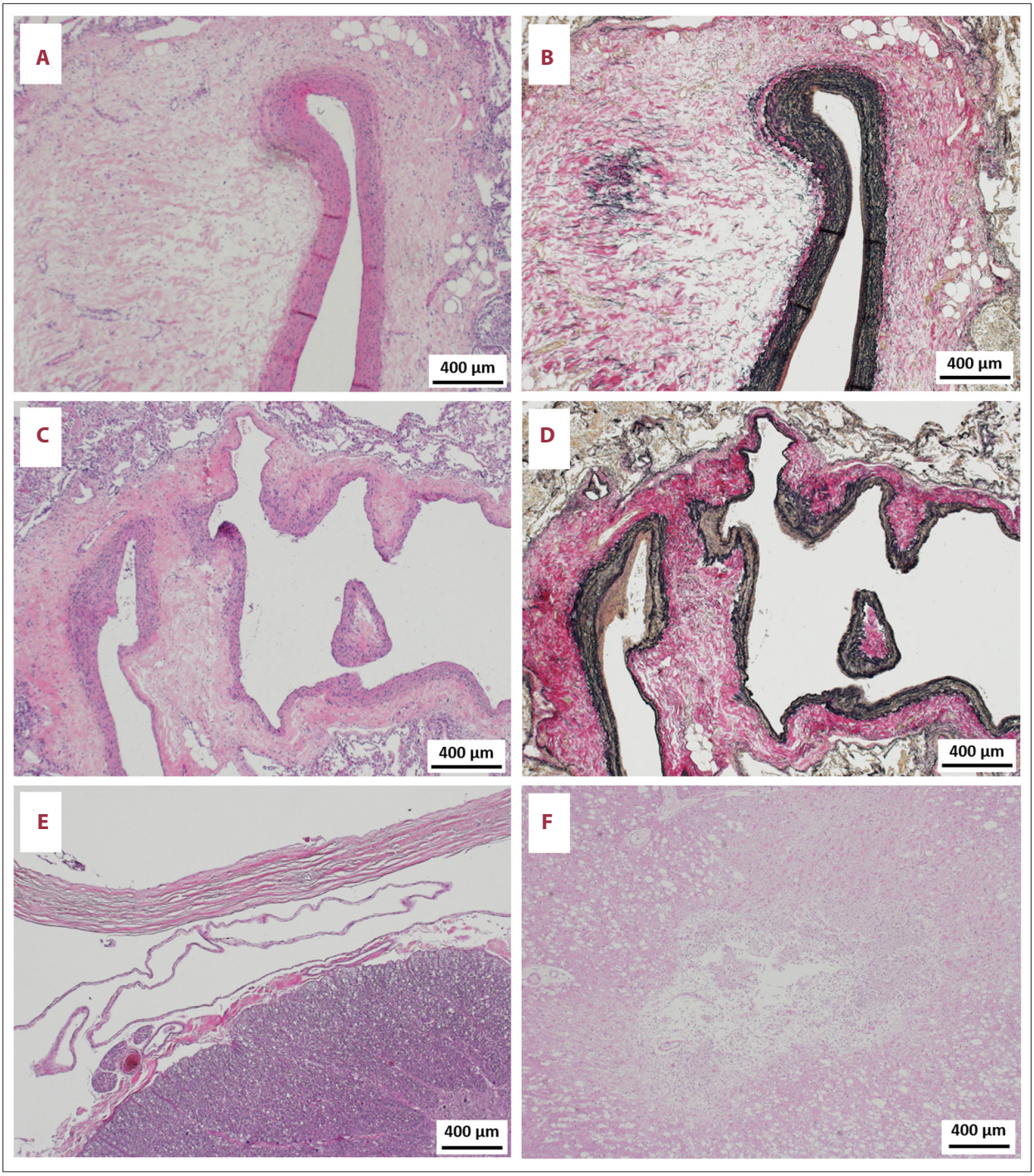

Figure 7. Autopsy findings. No inflammatory cells were found around the arteries (**A, B**) or veins (**C, D**), but some parts still had intimal hypertrophy and adventitial fibrosis. Pachymeninx indicating hypertrophic pachymeningitis (**E**). Brain parenchyma indicating loss of neurons with gliosis spreading at the gray mater (**F**). Magnification: **A**, 40× (H&E); **B**, 40× (EVG); **C**, 40× (H&E); **D**, 40× (EVG); **E**, 40× (H&E); **F**, 40× (H&E).

up to 65% of patients have multiple nodules, but they can be solitary [17]. The nodules and masses of GPA can range from a few millimeters to >10 cm in diameter [16]. Pathologically, the nodules and masses in GPA are composed of vasculitis, parenchymal necrosis, or granulomatous inflammation [11,18]. In our case, the clinical presentation of pulmonary nodules and masses resembled that of GPA; however, the diagnostic criteria for GPA were not satisfied [12], as the pathology of the

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Table 1. Summary of the patient's presentations comparing clinical feature of GPA and BD, and other differential diagnosis in rheumatic diseases.

Patient' presentations	Comparison to GPA	Comparison to BD	Other differential diagnosis in rheumatic diseases
Fever	Compatible	Compatible	FMF or many other rheumatic diseases
Episcleritis	Compatible (clinically)	Not typical (typically uveitis)	RA, SLE, GCA, PN, Cogan's syndrome
Thrombophlebitis	Rare	Compatible (clinically/ pathologically)	APS, Buerger disease
Deep vein thrombosis	Increasing risk (36,37)an increased incidence of venous thromboembolism (VTE	Compatible (clinically)	APS, Hughes-Stovin syndrome
Pulmonary nodules/ mass	Clinically compatible/ Pathologically incompatible	Incompatible (clinically)	IgG4-related disease
Cerebral lesions	Compatible (clinically)*	Compatible (clinically/ pathologically)	None
Hypertrophic pachymeningitis	Compatible (clinically/ pathologically)	Rare (reported in only one case (33))	RA, Sjögren's syndrome
Negative findings for typical features of GPA or BD	No history of ENT findings No history of peripheral neuropathy No history of glomerulonephritis Negative for granulomatous inflammation Negative for ANCA	No history of oral aphthosis No history of uveitis No history of genital ulcer No history of epididymitis No history of inflammatory bowel disease No history of arterial aneurysm No history of joint inflammation Negative pathergy test No risk of human leukocyte antigen	

* Histopathological finding is previously unreported. GPA – granulomatosis with polyangiitis; BD – Behçet's disease; FMF – familial Mediterranean fever; RA – rheumatic arthritis; SLE – systemic lupus erythematosus; GCA – giant cell arteritis; PN – polyarteritis nodosa; APS – antiphospholipid syndrome ENT – ear nose throat; ANCA – anti-neutrophil cytoplasmic antibody.

antemortem biopsy of the lung was inconsistent with GPA. Vasculitis affecting medium-to-small veins and arteries without necrotizing vasculitis or granulomatous inflammation has never been reported. Moreover, the findings of fibrosis with lymphocyte and plasmacyte infiltration in the pulmonary alveoli were inconsistent with GPA. This intra-alveolar finding mimicked histologically lymphoplasmacytic-type inflammatory pseudotumors [19] caused by IgG4-related disease [20]; however, the serum IgG4 levels were not elevated, and no IgG4-positive plasmacyte infiltration was noted by immunostaining.

The second characteristic finding in our case was intracranial vasculitis with HP and cerebral lesions. NBD was considered as a differential diagnosis according to head MRI manifestations and pathological findings on autopsy. NBD is subcategorized into parenchymal NBD (P-NBD) and nonparenchymal NBD (NP-NBD) types[21]. Furthermore, P-NBD is subdivided into acute P-NBD (A-P-NBD) and chronic progressive P-NBD (CP-P-NBD) [22,23]. A-P-NBD is characterized by acute meningoencephalitis with or without focal lesions. MRI of the focal lesions demonstrates hyper-intensity on DWI and T2WI, and the lesions are commonly enhanced on Gad-T1WI [21]. CP-P-NBD is characterized by slowly progressive dementia and ataxia with persistent elevation of CSF IL-6 (≥20 pg/mL), and progressive brainstem atrophy on MRI [21–24]. The brain pathology in A-P-NBD is perivasculitis characterized by perivascular infiltration of lymphocytes and neutrophils with or without signs of necrosis. In later stages, inflammatory infiltration is less prominent, and axonal loss and gliosis predominate [21,25]. In our case, histopathological findings of small necrotic foci with gliosis met the criteria for NBD. Furthermore, A-P-NBD is more likely than CP-P-NBD because of the CSF IL-6 levels (14.4 pg/mL) and the absence of brainstem atrophy. Varying patterns were observed on MRI throughout the patient history:

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(a) hyper-intensity on T2WI at the globus pallidus, (b) ring-enhancing lesion with central hyper-intensity on DWI, and (c) multiple patchy hyper-intense areas on DWI, T2WI, FLAIR, and Gad-T1WI. The findings of (a) and (c) correspond to the presentation of A-P-NBD, whereas those of (b) may correspond to NBD, as some case reports described NBD causing ring-enhancing lesions [26–29]. Nishino et al. reported that GPA can cause cerebritis, but it is rare among the other neurological manifestations in GPA (approximately 4%) [30]. MRI manifestations of cerebritis in GPA are reported as DWI restriction and patchy high T2 signals [31], but HP is a rare condition in NP-NBD [21,32]; however, a case report described HP in NBD, suggesting an association [33].

The third characteristic point was that the patient's vasculitis was not only arteritis but also phlebitis presented as thrombophlebitis, DVT, and pulmonary vasculitis. Vasculitis with no predominant type of vessel involved that can affect vessels of any size and type (arteries, veins, and capillaries) is included in the category of "variable vessel vasculitis" in the CHCC definitions, which comprises only BD and Cogan's syndrome [2]. Thrombophlebitis and extensive DVT are common in BD, but the pulmonary presentation does not correspond to BD, and the diagnostic criteria for BD [4,5] were not satisfied. Cogan's syndrome was also excluded because audiovestibular symptoms were not present [34,35].

The limitation of our approach and conclusions is that evidence from autopsy samples supporting vasculitis remained insufficient because the active phase had already passed when the autopsy was performed. Antemortem biopsies of brain parenchyma were not performed because the patient's condition prevented invasive study; therefore, consistency between the autopsy and antemortem status cannot be confirmed. The autopsy of the lungs was consistent with the antemortem biopsies because the autopsy findings of intimal hypertrophy and adventitial fibrosis in the arteries were considered to be healed vasculitis. According to our observations, more cases should be analyzed to clarify the characteristics of the disease.

Conclusions

This is the first case report of an unclassified vasculitis, which was characterized by medium-to-small-sized arteritis and phlebitis without necrotizing vasculitis or granulomatous inflammation, causing relapsing fever, episcleritis, thrombophlebitis, DVT, pulmonary vasculitis, and intracranial vasculitis. The clinical conditions share some similarities with GPA and BD; however, no classification criteria for any specific vasculitis were met. More cases need to be analyzed to confirm our findings.

Conflict of interest

None.

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