Diagnostic Procedures for Vasculitis

Toshiharu Matsumoto, MD
Clinical Professor of Department of Diagnostic Pathology
Juntendo University Nerima Hospital, Tokyo, Japan

Introduction

In 1994, the International Chapel Hill Consensus Conference Nomenclature of Vasculitides was published,[1] and this classification has been used internationally. Recently, the classification was revised as the "2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides". [2]

In Japan, many excellent studies of vasculitis had previously been published, so the first international meeting of vasculitis in Japan (The Asia Pacific Meeting of Vasculitis and ANCA Workshop 2012; AP-VAS) was held in Tokyo in 2012. The consensus of AP-VAS led to the conclusion of the revision of the International Chapel Hill Consensus Conference Nomenclature of Vasculitides. On the other hand, 18 years ago, the "Research Meeting of Vasculitis" was started and, in this meeting, pathological findings and diagnostic procedures for vasculitis have been discussed. In 2005, the "Atlas of Vasculitis", in which detailed clinical and pathological findings are described, was published by the Research Committee of Vascultis of the Ministry of Health, Labour and Welfare in Japan.[3]

In this lecture, I will take about diagnostic procedures for vasculitis from a pathological aspect, based on my experiences, the "Research Meeting of Vasculitis" , the "Atlas of Vasculitis in 2005", and others.

General Procedures for Diagnosis of Vasculitis

The evaluation of pathological findings is the most important factor for the diagnosis of vasculitis. The pathological evaluation of vasculitis should volve the following steps. Firstly, the evaluation of vasculitis is made according to the size of vessels: large arteries, medium-sized arteries, and small vessels, because primary vasculitis in large and medium-sized veins is exceedingly rare. The confirmation of histological findings of vasculitis at each size is very important. Secondly, necrotizing and granulomatous arteritides are frequent and characteristic vasculitides, so the presence or absence of both types is important. Also, evaluation of the type of inflammatory cell is important; intense eosinophilic infiltrate occurs in eosinophilic

granulomatosis with polyangiitis (Churg-Strauss/ EGPA), and neutrophilic infiltrate and nuclear debris are found in leukocytoclastic vasculitis. The diagnosis of vasculitis should be based on pathological findings plus clinical data (age, gender, clinical symptom, detection of auto-antibody, and others).

Vasculitis in Vessels of Each Size

1. Large Arteries

Takayasu arteritis (TAK) and giant cell arteritis (GCA) are the principle disorders.[2-4] Both vasculitides predominantly affect large arteries, especially the aorta and/or its major branches. GCA has a predilection for branches of the carotid and vertebral arteries, and often involves the temporal arteries, so biopsy of temporal artery is routine for the pathological diagnosis of GCA. Both vasculitides show granulomatous artertitis, and histological differentiation between them is very difficult, but TAK has a more complex histology compared with GCA, such as proliferation and thickening of the vasa vasorum. In addition, the age is important for the differentiation; younger than 50 years in TAK and older than 50 years in GCA.

Behçet's disease (BD) associated with lage vascular lesions is called vasculo-BD.[5] Vasculo-BD predominantly affects the aorta and its branches. The type of arteritis is usually active or scarred arteritis without granuloma, but, rarely, granulomatous arteritis with a similar histology to TAK occurs.[5] Differential diagnostic points between vasculo-BD and TAK are the presence or absence of symptoms compatible with BD (aphthous stomatitis, genital ulceration, and uveitis) and the detection of venous occlusion in large veins (this phenomenon in BD).[5]

2. Medium-sized Arteries

Kawasaki disease (KD) and polyarteritis nodosa (PAN) are included. Professor Takahashi will lecture on KD.

PAN presents with necrotizing arteritis in medium-sized arteries and the frequent involvement of small arteries without glomerulonephritis, and is not associated with antineutrophil cytoplasmic antibodies (ANCAs).[2,3] Organ involvement of PAN frequently occurs in the liver, spleen, gastrointestinal tract, genital system, gallbladder, kidney, and lungs.[6] For the histological classification of PAN, Arkin's classification is widely used: 1st stage, degenerative stage; 2nd stage, acute inflammation stage; 3rd stage, granulation tissue stage; 4th stage, healed granulation tissue stage.[7] Generally, the 1st and 2nd stages are the acute stage, and 3rd and 4th stages are the healed stage. Isolated

necrotizing arteritis (INA) is the vasculitis that should be differentiated from PAN. In INA, necrotizing arteritis, predominantly in medium-sized arteries, occurs in a single organ (single-organ vasculitis: SOV), especially the genital system, gallbladder, and gastrointestinal tract, and these findings are very similar to those of PAN.[2-4,8] Differential diagnostic points between PAN and INA are clinical findings indicating inflammatory reactions throughout the body (present in PAN) and aneurysmal formation in affected arteries (occasionally present in PAN).[8] In SOV, the usual form is necrotizing arteritis, but granulomatous arteritis rarely occurs.[4] In the granulomatous arteritis case of SOV, the absence of both clinical findings of inflammation throughout the body and findings indicating vasculitis in other organs is the diagnostic points differentiating it from other granulomatous arteritides, such as localized TAK and granulomatosis with polyangiitis, (Wegener's/ GPA) .

3. Small Vessels

Vasculitis affecting small vessels (small vessel vasculitis: SVV) divided into ANCA-associated vasculitis (AAV) and immune complex SVV.[2]

AAV predominantly affects small vessels and associates with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. It consists of microscopic polyangiitis (MPA), GPA, and EGPA. MPA is diagnosed if there is necrotizing arteritis in small arteries. However in cases with SVV plus PAN- type arteritis in medium-sized arteries throughout the body, the mixed type of MPA and PAN is better for the diagnosis. In GPA cases, biopsy samples from the upper respiratory tract offer a pathological division, and histological diagnostic points of GPA in such materials are the detection of map-like necrosis, granulomatous inflammation, giant cells, and micro-abscesses.[3] In EGPA cases, muscle biopsy is performed for the diagnosis and, in such material, the presence of necrotizing arteritis in small arteries with intense eosinophlic infiltrate leads to the diagnosis of EGPA.

Immune complex SVV consists of anti-glomerular basement membrane (anti-GBM) disease, cryoglobulinemia vasculitis (CV), IgA vasculitis (Henoch-Schönlein/ IgAV), and hypocomplementemic urticarial vasculitis (HUV).[2] Among them, IgAV is the most common disorder and, IgAV is frequently diagnosed by the detection of necrotizing arteritis and/or leukocytoclastic vasculitis in small vessels with IgA deposition in the vessel wall on skin biopsy.[2,3]

Vasculitis Associated with Systemic Disease

Rheumatoid (rheumatoid artheritis: RA) vasculitis and lupus (systemic lupus erythematosus: SLE) vasculitis are the main disorders in this category.[2] Rheumatoid vascultis consists of cutaneous leukocytoclastic vasculitis and generalized arteritis.[3] Generalized arteritis predominantly affects medium-sized arteries, and is classified into the PAN type, endoarteritis (EA) type, and rheumatoid arthritis (RA) type.[3] The PAN type is the most common type, and the EA type is thought to be the scarred stage of the PAN type. The RA type is rheumatoid nodule formation in the vessel wall, and it is very rare. RA with intense generalized arteritis is diagnosed as malignant RA (MRA). In MRA, arteritis predominantly occurs in intestinal walls, and occasionally leads to perforation by ischemia due to arteritis.

Lupus vasculitis consists of PAN type arteritis affecting predominantly medium-sized arteries.[9] On the other hand, antiphospholipid antibodies (APL), which include lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL), are frequently found in patients with SLE.[10] APL presence is associated with arterial/venous thrombosis and recurrent pregnant loss. These clinical manifestations with the presence of APL are recognized as antiphospholipid syndrome (APS). In APS, thrombosis usually occurs, but, rarely. overlapping of PAN type necrotizing arteritis is found.[3] In our experiences of 47 placental tissues from 47 pregnant SLE patients with and without APL, the incidence of extensive infarction, decidual vasculopathy, decidual thrombosis, and perivillous fibrinoid change, which have been thought to be characteristic lesions of APL placenta, was significantly higher in LAC and aCL double-positive patients than in patients without APL.[11] Extensive infarct leads to fetal death, so our study indicates that LAC and aCL double-positivity is an important risk factor for fetal death in SLE patients.[11] These findings are useful for the evaluation of SLE placenta.

Segmental Arterial Mediolysis

Segmental arterial mediolysis (SAM) was discussed in the “Research Meeting of Vasculitis”. SAM was first described by Slavin and Gonzalez-Vitale in 1976.[12] This disease is rare, but a recognition of SMA is needed to identify the cause of massive intra-abdominal hemorrhage. SAM was observed in a large abdominal muscular artery, and the salient histological feature of this arterial lesion is partial or total mediolysis. This is accompanied by linear fibrin deposition between the media and adventitia and a variable nonpleomorphic inflammatory infiltrate. Total mediolysis leads to the formation of arterial gaps. A dissecting aneurysm frequently occurs and leads to massive intra-abdominal hemorrhage.

Conclusions

To diagnose vasculitis, an awareness of the pathological findings in each disease is the most important point. Also, an overall evaluation with the addition of clinical information is also needed.

References

1. Jennette JC, Falk RJ, Andrassy K, et al: Nomenclature of systemic vasculitides: the proposal of an international consensus conference. Arthritis Rheum 37:187-192, 1994
2. Jennette JC, Falk RJ, Bacon PA, et al: 2012 revised international Chapel Hill consensus conference nomenclature of vasculitedes. Arthritis Rheum 65:1-11, 2013
3. Research Committee of Vasculitis in Ministry of Health, Labour and Welfare in Japan, Atlas of Vasculitis, eds by S Ozaki, T Yoshiki, 2005
4. Vuong PN, Berry C. Vasculitis in The Pathology of Vessels, Springer-Verlag France, Paris, 2002, pp237-288
5. Matsumoto T, Uekusa T, Fukuda Y: Vasculo-Behçet's disease: A pathological study of eight cases. Hum Pathol 22:45-51, 1991
6. Matsumoto T, Homma S, Okada M, et al: The lung in polyarteritis nodosa: A pathologic study of 10 cases. Hum Pathol 24:717-724, 1993
7. Arkin A: A clinical and pathological study of periarteritis nodosa. A report of five cases, one histologically healed. Am J Path 6:401-426, 1930
8. Matsumoto T, Kobayashi S, Ogishima D, et al: Isolated necrotizing arteritis (localized polyparteritis nodosa): examination of the histological process and disease entity based on the histological classification of stage and histological differences from polyarteritis nodosa. Cardiovascular Pathol 16:92-97, 2007
9. Matsumoto T, Yoshimine T, Shimouchi K, et al: The liver in systemic lupus erythematosus: Pathological analysis of 52 cases and review of Japanese autopsy registry data. Hum Pathol 23:1151-1158, 1992
10. Hughson MD, McCarty GA, Brumback RA: Spectrum of vascular pathology affecting patients with the antiphopholipid syndrome. Hum Pathol 26:716-724, 1995
11. Ogishima D, Matsumoto T, Nakamura Y, et al: Placental pathology in systemic lupus erythematosus with antiphospholipid antibodies. Pathol Int 50:224-229, 2000
12. Slavin RE, Gonzalez-Vitale JC: Segmental mediolytis arteritis. A clinical pathologic study. Lab Invest 35:23-29, 1976