OPEN ACCESS Freely available online

Internal Medicine: Open Access

Case Report

Explosive Granulomatosis with Polyangiitis Mimicking Infective Endocarditis

Lisa Shue[1], Maggie Chow[1], Brandon Cohen[1], David Peng[2*]

[1]Department of Dermatology, Keck School of Medicine of USC, University of Southern California, USA;2Department of Dermatology, Norris Comprehensive Cancer Center, Keck School of Medicine of USC, University of Southern California USA

ABSTRACT

Background: Granulomatosis with polyangiitis (GPA) is a rare systemic disease that causes necrotizing granulomatous inflammation of small- and medium-sized blood vessels. Infective endocarditis (IE), which is a disease due to infection of the innermost surface of the heart, is pathophysiologically distinct from GPA and yet these two entities can manifest in strikingly similar ways.

Case presentation: We report a case of a 46-year-old male whose presentation and history were strikingly suggestive of IE but was ultimately diagnosed with GPA. Originally, he presented with fever, oral ulcers, and purpuric lesions on the extremities. The patient had a history of illicit drug use and had recently undergone a dental procedure one week prior to presentation, which were classic risk factors for IE. His fever and respiratory difficulty were unresponsive to antibiotic therapy. His respiratory and renal status declined explosively during his hospitalization, requiring intubation and intensive level care. His clinical progression, negative blood cultures, and a positive c-ANCA screen prompted a workup that was more consistent with GPA. Administration of anti-inflammatory medications and plasmapheresis eventually lead to the resolution of his symptoms. Because of his precipitous pulmonary decline, his outcome would have been poor if the correct diagnosis of GPA were to have been overlooked.

Conclusions: ANCA-associated vasculitis and infective endocarditis can demonstrate similar clinical findings, including in the skin. Overlap in serologic markers and other organ involvement can lead to difficulty in distinguishing these two diseases, which require contrasting treatment methods. We highlight and compare the similarities and differences between GPA and IE in discussion of this interesting case to emphasize the importance of being clinically vigilant in differentiating these two separate disease processes.

Keywords: Granulomatosis with polyangiitis; Infective endocarditis; c-ANCA; Wegener's granulomatosis

Abbreviations: GPA: Granulomatosis with Polyangiitis; IE: Infective Endocarditis; ANCA: Antineutrophil Cytoplasmic Antibodies; PR-3: Proteinase-3

INTRODUCTION

Wegener's granulomatosis, recently renamed as granulomatosis with polyangiitis (GPA), is a disease characterized by multifocal necrotizing granulomatous inflammation of small- and medium-sized blood vessels. GPA is a rare disease with an estimated worldwide annual incidence of 3.0-14.4 per million individuals [1]. It is most commonly observed among middle-aged Caucasian individuals, but has been reported in other ethnic populations [2]. GPA is strongly associated with the presence of antineutrophil cytoplasmic antibodies (ANCA) and is classified as part of a group of ANCA-associated vasculitides [3]. Specifically, Proteinase-3/c-ANCA (PR-3/c-ANCA) is a biological marker of GPA with a sensitivity and specificity of >90% [4].

Symptoms of GPA most classically involve the upper and lower respiratory tract and kidneys. However, the clinical presentation can be varied and can affect any organ system. Initial disease manifestations may be non-specific, often result in a delay in

***Correspondence to:** David Peng, Department of Dermatology, Norris Comprehensive Cancer Center, Keck School of Medicine of USC, University of Southern California, USA , E-mail: David.Peng@med.usc.edu

Received date: January 3, 2019; **Accepted date:** February 28, 2019; **Published date:** March 07, 2019

Citation: Shue L, Chow M, Cohen B, Peng D (2019) Explosive Granulomatosis with Polyangiitis Mimicking Infective Endocarditis. Intern Med 9:302. doi: 10.35248/2165-8048.19.9.302.

diagnosis. These manifestations typically include upper respiratory tract complaints, such as oral ulcers or chronic sinusitis, and non-specific constitutional symptoms such as fever, night sweats, and weight loss [1]. Other known presentations of GPA include vasculitic skin lesions, joint involvement, ear, nose, throat symptoms, peripheral neuropathy, and cardiac involvement including pericarditis, cardiomyopathy, coronary artery disease, and valvular disease [2,5,6]. Diagnostic criteria proposed by the American College of Rheumatology that should raise suspicion of GPA include nasal or oral inflammation, pulmonary nodules or cavities, active urinary sediment, and granulomatous inflammation on biopsy [1].

In the absence of treatment, GPA is usually fatal within one year [1]. Cause of death is often secondary to pulmonary and renal complications [2]. However, with the use of immunosuppressive therapies, disease remission readily occurs. Initial therapy often includes glucocorticoids in combination with cyclophosphamide or rituximab [1,7,8]. Depending on disease severity, supplemental plasma exchange may be considered [9,10]. Maintenance therapies include rituximab, methotrexate, azathioprine, and/or mycophenolate [8,11,12].

In contrast, infective endocarditis (IE) is a disease caused by infection of the endocardial surface of the heart, often due to *streptococci*, *staphylococci*, or *enterococci* pathogen species [13]. Bacteria or fungi in the blood attach to the endocardium and cause endothelial injury, causing recurring damage and bacterial adherence. Eventually, a dense aggregate of microorganisms, leukocytes, and platelet-rich thrombi is formed in the cardiac endothelium known as a "vegetation", which is detectable on echocardiography and is considered a major criteria of evidence in diagnosing IE [14]. The infective vegetations can lead to septic emboli causing vascular pathology such as purpura in the skin as well as strokes, pulmonary infarcts, mycotic aneurysms, and conjunctival and intracranial hemorrhages. Risk factors for IE include the presence prosthetic valves or cardiac devices, valvular heart disease, intravenous drug abuse, indwelling intravenous lines, and recent dental or surgical operations [14].

We report a case of a 46-year-old male who was originally thought to have infective endocarditis but was ultimately diagnosed with GPA. The overlap in clinical findings between these two disease processes is compared and discussed.

CASE REPORT

A 46-year-old male with history of maxillary squamous atypia, bilateral pulmonary nodules suspicious for metastasis, illicit drug use, and recent tooth extraction presented with fever, purple distal digits, and oral ulcers. Dermatology was consulted to evaluate his multiple purpuric lesions. On examination, the patient had oral ulcers of the tongue and lower lip; splinter hemorrhages; purpuric macules and patches over the knuckles, fingertips, and toes; distal purpura; and Janeway lesions, as shown in Figure 1. The patient's history of illicit drug use and recent tooth extraction along with his clinical presentation were concerning for infective endocarditis (IE).

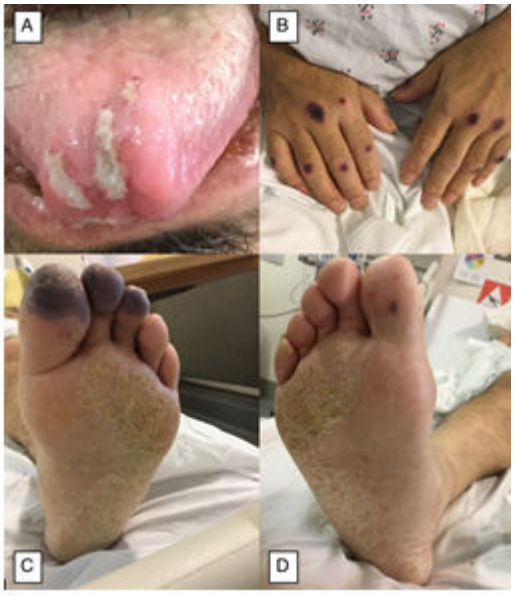

Figure 1: A) Oral ulcerations of the tongue and lower lip; B) Splinter hemorrhages of the nailbeds and purpuric patches on the joints of the hand; C) Distal purpura of the lower extremity; D) Janeway lesions on the sole of foot.

Upon admission, patient's labs were notable for leukocytosis, thrombocytosis, elevated ESR and CRP, and elevated creatinine. Patient was initially treated with broad-spectrum empirical antibiotics. Two days later, patient developed a fever despite being on multiple antibiotics. Blood cultures were negative. In addition, the transthoracic echocardiogram was not remarkable for vegetations or valvular abnormalities. Based on recommendations by the dermatology consult service for workup of other causes of leukocytoclastic vasculitis, a PR-3/c-ANCA screen was elevated at 503.9 AI (reference range: <1.0=no antibody detected; >or=1.0=antibody detected). This prompted a rapid rheumatologic workup.

Upon original presentation patient denied any shortness of breath. However, over his hospitalization he developed worsening dyspnea and bloody sputum, unexpectedly and rapidly decompensating on day 5 requiring intubation. A bronchoscopy with BAL was performed with findings of diffuse inflammation and necrotic foci, with right lateral distal tracheal wall mass concerning for possible inflammatory pseudotumor consistent with GPA tracheobronchitis. The patient also had a steadily rising creatinine and positive urinalysis with presence of protein, hematuria, and coarse granular casts with decreased renal function during his hospital course. Due to the negative infectious workup, positive c-ANCA result, and worsening respiratory and renal symptoms highly suggestive of GPA vasculitis, patient was started on Solumedrol, Rituxan, and plasmapheresis which eventually lead to clinical improvement over the course of 1 month.

DISCUSSION

Our patient originally presented with chief complaints of worsening oral and throat pain for 1 week, and progressive extremity skin discoloration and ulceration for 2 weeks. The

patient was a drug user with a recent tooth extraction, and his history of illicit drug abuse and recent dental procedure are both considered traditional risk factors for bacteremia-induced IE [13]. Additionally, IE classically has a dermatologic presentation of splinter hemorrhages of the fingernail beds and macular hemorrhagic lesions of the extremities, all of which the patient had [15]. However, due to his rapidly progressive pulmonary disease, his outcome would have been poor if the eventual correct diagnosis of GPA were to have been missed.

The prevalence of cutaneous manifestations in GPA is reported between 35%-50% [16]. Skin involvement may be the initial clinical presentation of the disease in about 10% of the time, and it usually indicates active systemic disease [16-18]. Some of the more commonly seen skin lesions in GPA include palpable purpura, papulonecrotic lesions, and ulcers, including of the oral mucosa. The lower extremities are commonly affected [16,18-20]. Oral lesions have been reported to occur in up to 62% of cases [21] and may be the initial presenting sign in 5%-6% of cases [1]. Oral manifestations include erosions or ulcerations on the buccal or lingual mucosa, mucosal nodules, hyperplastic gingivitis ("strawberry gingiva"), and rarely fistula development [1,21]. Histopathologically, a common finding of GPA cutaneous lesions is leukocytoclastic vasculitis [17,22]. Other findings include granulomatous inflammation, dermal and epidermal necrosis, nonspecific ulceration, subcutaneous nodules, urticaria, and less often erythema nodosum and pyoderma gangrenosum-like lesions [16,22,23]. The presence of cutaneous findings has been proposed to correlate with presence of renal disease [16]. Though these cutaneous features can be suggestive of GPA, many overlap with those of IE.

Various dermatological lesions suggestive of vascular phenomena may also be indicative of septicemia secondary to IE. Cutaneous lesions in infective endocarditis occur secondary to septic emboli and/or immunologic response to infection resulting in immune complex deposition. Purpura, splinter and conjunctival hemorrhages, Janeway lesions, and Osler nodes are examples of such suggestive skin findings, which can closely resemble the skin manifestations of GPA [24,25]. Vascular purpura is the more typically seen dermatological finding of IE and is most often found on the lower parts of the body such as the legs and back [25]. The overall frequency of cutaneous lesions amongst IE cases varies between 5% to 25%, though none of them are pathognomonic for endocarditis [24,25]. Histologically, lesions show findings of septic emboli with associated inflammatory response or leukocytoclastic vasculitis [25,26].

Given that both entities present with overlapping dermatologic presentations, the differentiation of these two entities provides a diagnostic challenge. Table 1 compares the differences and similarities between these two distinct clinical diagnoses. Leukocytoclastic vasculitis is a common histological finding between the cutaneous lesions of both diseases [17,22,25,26]. The presence of purpura and necrotic skin lesions may be present in either disease, and their correct interpretation can be challenging. Splinter hemorrhages are also a non-specific finding in both conditions [14,20]. Incorrect interpretation of GPA-associated purpuric nodules as IE-associated Osler's nodes has been documented previously [4].

Table 1: shows the similarities and differences in clinical presentation and laboratory findings for patients with ANCA-associated vasculitis versus patients with ANCA-positive bacterial endocarditis [3].

	ANCA-associated vasculitis	Bacterial endocarditis
Constitutional symptoms [3]	Frequent	Frequent
Organ involvement [3,29,31]	Kidneys and lungs classically, may also affect skin and peripheral nerves	Often limited to skin and kidneys, with rare lung involvement
Spleen involvement [32,34]	Rare	Frequent
Complement levels [3]	Normal	Low
Circulating immune complexes [3]	Absent	Present
Other autoantibodies [3,29]	Rare	Frequent (likely from polyclonal non-specific B-cell activation)
ANCA positivity [3,27]	Persistent	Transient, resolves with antibiotics
Blood culture	Negative	Positive
Valve involvement [3]	Aortic 100%	Aortic 62.5%
	Mitral 18.2%	Mitral 37.5%

	Both 18.2%	Both 12.5%
Vegetations on echocardiography [3,30]	Rare; small	Highly associated; large
Need for valve replacement [3,38]	Almost always	Uncommon

Further, ANCA-positive IE has been documented, making the differential diagnosis between IE and ANCA-associated vasculitis even more complex [3,27-31]. It has been suggested that the presence of ANCA in IE reflects the systemic inflammation and polyclonal non-specific immunoglobulin production from persistent B cell stimulation secondary to chronic infection, as opposed to ANCA having any direct contribution to IE pathogenesis [27,31,32]. ANCA positivity in infective endocarditis may occur due to non-specific B-cell activation or autoimmunization after release of PR-3 from neutrophils [33]. In IE, ANCA titers revert to negative after antibiotic treatment [33].

Renal disease, a classic presentation of GPA, is also a well-known sequela of IE affecting up to 40%-50% of IE patients [28]. Interestingly, IE associated with ANCA positivity is correlated with more frequent renal impairment [29]. One way of distinguishing between GPA and ANCA-positive IE in a patient with renal disease is that patients with GPA more commonly have respiratory or nervous system involvement, and IE patients are more likely to have splenomegaly and/or hepatomegaly [34]. However, clinicians should remain vigilant that respiratory involvement noted as pulmonary infiltrates or nodules in ANCA-positive bacterial endocarditis cases have been reported, [33,35] which overlaps with the characteristic respiratory symptoms of GPA. Lung involvement in IE is frequently diagnosed as lung abscess, but can also show alveolar capillaritis resembling ANCA-associated vasculitis [33]. Similarly, while splenic involvement is considered to be a well-known sequela of bacterial endocarditis, rare cases of splenomegaly and infarction related to GPA have been described [36].

Cardiac abnormalities in GPA range from 3% to 44%, with the most common abnormality being pericarditis [5,36]. In a large retrospective cohort study analyzing the frequency of cardiac involvement in GPA, pericarditis was present in 35% of GPA patients with cardiac manifestations, followed by cardiomyopathy (30%), coronary artery disease (12%), and valvular disease (6%) [5]. Valvular disease in GPA most frequently involves the aortic valve, causing vegetations and regurgitation which can clinically resemble infective endocarditis [37,38]. It has been proposed that apparent vegetations occur secondary to granulomatous inflammation of the valve resulting in myxoid degeneration [39]. However, discrete large vegetations detected on echocardiography suggest bacterial endocarditis, in contrast to discrete small vegetations suggesting ANCA-associated vasculitis [3,32]. Furthermore, mitral valve involvement is more commonly seen in bacterial endocarditis versus ANCA-associated vasculitis, which seems to preferentially affect the aortic valve [3].

The combination of overlap in ANCA positivity, cutaneous vasculitic presentations, cardiac, pulmonary and renal involvement can make distinguishing IE and GPA a true clinical challenge. For clinically ambiguous cases, blood cultures may be the primary differentiating factor between GPA and IE as they are positive in 90% of cases of IE [14].

CONCLUSION

In summary, GPA is a PR-3/c-ANCA-positive small vessel vasculitis with associated upper respiratory, lower respiratory, and renal involvement, as well as variable cutaneous findings. GPA and IE are both vascular disease processes that can demonstrate similar non-specific constitutional symptoms, cutaneous findings, serologic markers, and organ involvement, and therefore can be difficult to differentiate in certain settings. Due to the possible similarity in manifestation yet stark difference in pathophysiology of these two diseases, an unexpected response to therapy should alert the clinician of an alternate potential diagnosis as illustrated in our case. While GPA responds well to immunosuppression, IE would be exacerbated by immunosuppression. Thus, a thorough workup to distinguish GPA versus IE is crucial to avoid erroneously harming the patient.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

No identifying patient information provided.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LS performed a literature review and was the main contributor in writing the case report. MC advised and contributed to the discussion of the case report. All authors read and approved the final case report.

REFERENCES

1. Almouhawis HA, Leao JC, Fedele S, Porter SR. Wegener's granulomatosis: a review of clinical features and an update in diagnosis and treatment. J Oral Pathol Med. 2013;42:507-516.
2. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, et al. Wegener granulomatosis: An analysis of 158 patients. Ann Intern Med. 1992;116:488-498.
3. Chirinos JA, Corrales-MVF, Garcia S, Lichtstein DM, Bisno AL. Endocarditis associated with antineutrophil cytoplasmic antibodies: A case report and review of the literature. Clin Rheumatol. 2007;26:590-595.
4. Calachanis M, Ferrero P, Orzan F, Marchisio F, Trevi G. Vasculitis mimicking bacterial endocarditis. Ital Heart J. 2003;4:816-818.
5. McGeoch L, Carette S, Cuthbertson D, Hoffman GS, Khalidi N. Cardiac Involvement in Granulomatosis with Polyangiitis. J Rheumatol. 2015;42:1209-1212.
6. Tarzi RM, Pusey CD. Current and future prospects in the management of granulomatosis with polyangiitis (Wegener's granulomatosis). Ther Clin Risk Manag. 2014;10:279-293.
7. Mock M, Cerottini JP, Derighetti M, Buxtorf K, Livio F. Wegener's granulomatosis: Description of a case where cutaneous involvement was correlated with elevation of the c-ANCA titer. Dermatology. 2001;202:347-349.
8. Geetha D, Specks U, Stone JH, Merkel PA, Seo P. Rituximab versus clophosphamide for anca-associated vasculitis with renal involvement. J Am Soc Nephrol. 2015;26:976-985.
9. Kaplan AA. The use of apheresis in immune renal disorders. Ther Apher. 2003;7:165-172.
10. Jayne DRW, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18:2180-2188.
11. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. N Engl J Med. 2014;371:1771-1780.
12. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K. Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. JAMA. 2011;304:2381-2388.
13. Robinson AN, Tambyah PA. Infective endocarditis-An update for dental surgeons. Singapore Dent J. 2017;38:2-7.
14. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2016;387:882-893.
15. Pierce D, Calkins BC, Thornton K. Infectious endocarditis: Diagnosis and treatment. Am Fam Physician. 2012;85:981-986.
16. Daoud MS, Gibson LE, DeRemee RA, Specks U, El-Azhary, RA. Cutaneous Wegener's granulomatosis: Clinical, histopathologic, and immunopathologic features of thirty patients. J Am Acad Dermatol. 1994;31:605-612.
17. Walsh, John S, Gross DJ. Wegener's granulomatosis involving the skin. Cutis. 1999;64:183.
18. Francès C, Pagnoux C, Guillevin L. Dermatologic Manifestations of Granulomatosis with Polyangiitis (Wegener's Granulomatosis). In: Skin Manifestations in Rheumatic Disease. New York, NY: Springer New York. 2014;289-296.
19. Francès C, Du LTH, Piette JC, Saada V, Boisnic S. Wegener's Granulomatosis. Arch Dermatol 1994;130:861.
20. Patten SF, Tomecki KJ, Ohio C. Wegener's granulomatosis: Cutaneous and oral mucosal disease. J Am Acad Dermatol. 1993;28:710-718.
21. Manchanda Y, Tejasvi T, Ramam M, Handa R. Strawberry gingiva: A distinctive sign in Wegener's granulomatosis. J Am Acad Dermatol. 2003;49:335-337.
22. Barksdale SK, Hallahan CW, Kerr GS, Fauci AS, Stern JB. Cutaneous pathology in Wegener's granulomatosis. A clinicopathologic study of 75 biopsies in 46 patients. Am J Surg Pathol 1995;19:161-172.
23. Comfere NI, MacAron NC, Gibson LE. Cutaneous manifestations of Wegener's granulomatosis: A clinicopathologic study of 17 patients and correlation to antineutrophil cytoplasmic antibody status. J Cutan Pathol. 2007;34:739-747.
24. Tous-RF, Delgado-M AM, Gargallo-MV, Zarco-OC, Tous-Romero F. Cutaneous vasculitis: a presentation with endocarditis to keep in mind. An Bras Dermatol.2017;92:594-595.
25. Servy A, Valeyrie-Allanore L, Alla F, Lechiche C, Nazeyrollas P. Prognostic value of skin manifestations of infective endocarditis. JAMA Dermatology 2014;150:494.
26. Gomes RT, Tiberto LR, Bello VNM, Lima MAJ, Nai GA. Dermatologic manifestations of infective endocarditis. An Bras Dermatol. 2106;91:92-94.
27. McAdoo SP, Densem C, Salama A, Pusey CD. Bacterial endocarditis associated with proteinase 3 anti-neutrophil cytoplasm antibody. NDT Plus 2011;4:208-210.
28. Van HHS, Wilmes D, Aydin S, Clerckx C, Labriola L. Necrotizing ANCA-Positive Glomerulonephritis Secondary to Culture-Negative Endocarditis. Case Reports Nephrol 2015;2015:1-5.
29. Langlois V, Lesourd A, Girszyn N, Ménard J-F, Levesque H. Antineutrophil cytoplasmic antibodies associated with infective endocarditis. Medicine (Baltimore). 2016;95:e2564.
30. Tiliakos AM, Tiliakos NA. Dual ANCA positivity in subacute bacterial endocarditis. J Clin Rheumatol. 2008;14:38-40.
31. Mahr A, Batteux F, Tubiana S, Goulvestre C, Wolff M.Brief report: Prevalence of antineutrophil cytoplasmic antibodies in infective endocarditis. Arthritis Rheumatol. 2014;66:1672-1677.
32. Ying CM, Yao DT, Ding HH, Yang CD. Infective Endocarditis with Antineutrophil cytoplasmic Antibody: Report of 13 Cases and Literature Review. PLoS One. 2014;9:e89777.
33. Peng H, Chen WF, Wu C, Chen YR, Peng B. Culture-negative sub-acute bacterial endocarditis masquerades as granulomatosis with polyangiitis (Wegener's granulomatosis) involving both the kidney and lung. BMC Nephrol 13.2012.
34. Varnier GC, Sebire N, Christov G, Eleftheriou D, Brogan PA. Granulomatosis with polyangiitis mimicking infective endocarditis in an adolescent male. Clin Rheumatol. 2016;35:2369-7232.
35. Uh M, Mccormick IA, Kelsall JT. The journal of rheumatology positive cytoplasmic antineutrophil cytoplasmic antigen with pr3 specificity glomerulonephritis in a patient with subacute bacterial endocarditis. J Rheumatol. 2011;38:3-5.
36. Anthony DD, Askari AD, Wolpaw T, McComsey G. Wegener granulomatosis simulating bacterial endocarditis. Arch Intern Med. 1999;159:1807-1810.
37. Koyalakonda SP, Krishnan U, Hobbs WJ. A rare instance of multiple valvular lesions in a patient with Wegener's granulomatosis. Cardiology. 2010;117:28-30.
38. Espitia O, Droy L, Pattier S, Naudin F, Mugniot A. A case of aortic and mitral valve involvement in granulomatosis with polyangiitis. Cardiovasc Pathol. 2014;23:363-365.
39. Omoto T, Tedoriya T, Ishikawa N, Miyauchi T, Nagano N. Granulomatous endocarditis in a patient with Wegener's granulomatosis. J Cardiol Cases. 2011;4:e98-100.