A Patient with Rashes and Limb Weakness

S SAWHNEY*, M AGARWAL*, S ROY **, S BUXI , S SUD ***, AND S SINGH #

*From the *Pediatric Rheumatology Unit, Centre for Child Health, **Department of Histopathology, ***Department of Radiodiagnosis, North MRI Scan and Research Centre, Sir Ganga Ram Hospital, New Delhi, India, and #Department of Immunology, APCCC, PGI, Chandigarh, India.*

Correspondence to: Dr Sujata Sawhney, Pediatric Rheumatologist, B 602, Som Vihar, New Delhi 110022, India. drsujatasawhney@gmail.com

PATIENT SUMMARY

An 8-yr-old girl presented in July 2007 with a history of skin rashes during the last six months, pain and weakness of the left leg three months ago, one episode of loss of consciousness in the last three months and severe limb pains and worsening of the rashes over the last month (***Fig.*1**). The rash was erythematous, blanched on pressure, was not itchy and was predominantly seen on the hands and feet. There was no history of associated fever, weight loss, joint pains, oral ulcers, hair loss, respiratory or gastrointestinal complaints. There was no aggravating or relieving factor. No specific diagnosis was reached and the child was treated with antihistaminics. Until March 2007, the child had a spontaneous increase or decrease in the rashes with no associated complaints. At this time while playing she tripped, following which she could not bear weight on the left leg and was numb below the knee. Investigations included a hemoglobin level of 13 g/dL, leukocyte count of 10300/cu mm, platelets 248000/cu mm and an ESR of 30 mm at 1 hr. The CRP was negative, and transaminases and creatinine levels were normal. The creatine kinase was elevated to 3982 I.U/L (normal <140). The urine showed a 2+ proteinuria and 10 erythrocytes per high power field, urine culture grew *E. coli* 10000/mL. The rheumatoid factor, antineutrophilic cytoplasmic antibody (ANCA) and the antinuclear antibody (ANA) were negative. An MRI of the spine showed patchy signal alteration in the left gluteus, adductor group, rectus femoris and vastus lateralis muscles, compatible with that associated with history of trauma. The kidneys were swollen with altered signal intensity (***Fig.* 2**).Nerve conduction studies showed motor changes in the common peroneal, posterior tibial and sural nerve suggestive of a sciatic nerve injury. The child was treated with oral prednisolone for two weeks followed by tapering over next four weeks, during which she showed satisfactory improvement and resumed normal activities.

In May 2007, while playing she collapsed, accompanied by momentary loss of consciousness. A MRI of the brain showed multiple tiny foci of altered signal in the brain parenchyma in the right cerebellar hemisphere, pons, thalamus and left basal ganglia, suggestive of a "demyelinating process or vasculitis" **(*Fig.*3*a*** and **3*b***).

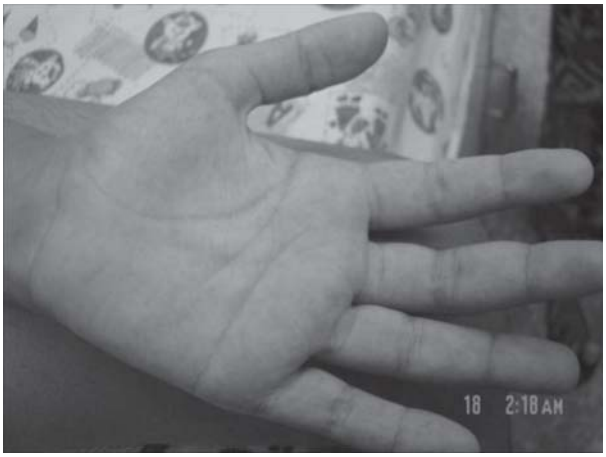

FIG. 1 *Erythematous rash on palms.*

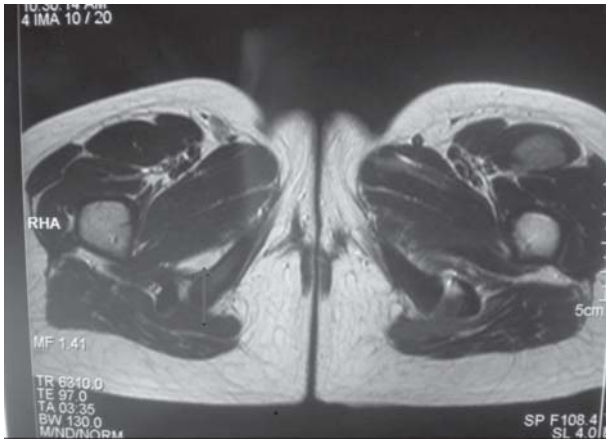

FIG. 2 *T2 weighted axial image showing a large area of hyperintensity in the rectus femoris muscle on the right side suggestive of inflammation.*

Over the next two months the child had an episodic increase in the rashes and limb pains. On examination at this hospital in July 2007, she had a blanching erythematous rash on the palms. The peripheral pulses and four limb blood pressures were normal. Investigations showed a hemoglobin level of 11.9g/dL, leukocyte count 9500/mm^3, platelet count 233000/mm^3 and an ESR of 20 mm at 1 hr. CRP was negative and urinalysis, liver function tests, creatinine and CPK were normal. The chest *X*-ray and thyroid function test were normal. The ANA, antiphospholipid antibodies, double stranded DNA and ANCA were negative, and complement levels were normal. A screen for infection with hepatitis B and C, and HIV was negative. Ultrasonography of the abdomen showed a scar on the superior pole of the right kidney. Nerve conduction velocity showed a delayed latency and decreased amplitude and conduction velocity in left sural nerve and only decreased amplitude in the left median nerve. The nerve conduction study was abnormal with left median motor axonal involvement and left sural sensory involvement with chronic neurogenic changes.

A diagnostic procedure was performed.

DISCUSSION

Dr. Surjit Singh: Clinical Discussant

Physical examination of the 8 yr old girl showed normal vital signs and four limb blood pressures. She had an erythematous palmar rash but the systemic examination was unremarkable. The reticulated rash was not classical of any particular disease but may be a manifestation of systemic vasculitis, antiphospholipid antibody syndrome or autonomic dysfunction. If persistent, such a rash should not be ignored. During evaluation, she had severe pain in the left leg and was noted to have abnormal nerve conduction study with left median motor axonal involvement and left sural sensory involvement with chronic neurogenic changes.

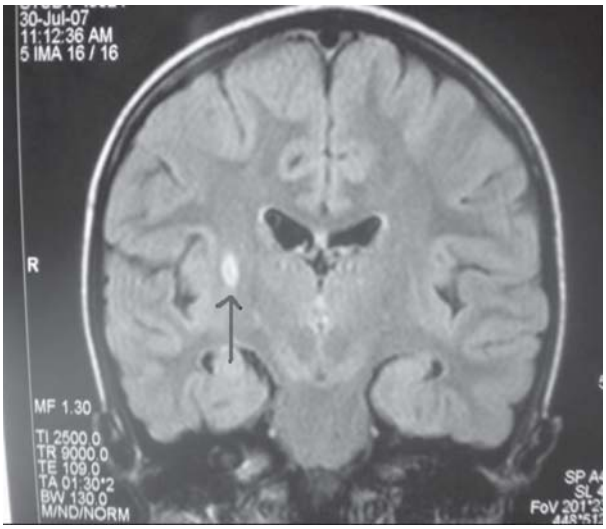

FIG. 3*a* *TIRM coronal image of the brain showing a focal hyperintense lesion on the right periventricular region suggestive of a lacunar infarct.*

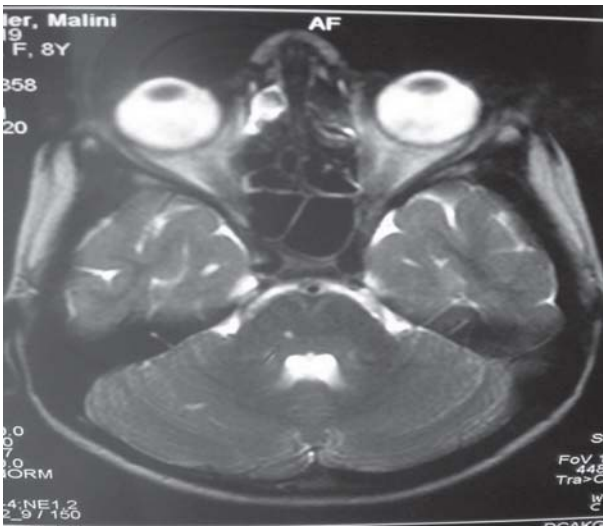

FIG. 3*b* *T2W axial brain MRI showing focal hyper intensity in the right side of the pons suggestive of a lacunar infarct.*

The patient appeared to have an episodic illness which was steroid responsive. In addition she also had a rash for many months, significant limb pain and muscle disease with pain and tenderness. Laboratory evaluation revealed a significantly elevated CPK level and MRI of the thigh muscles showed altered signal intensity in the anterior and lateral compartments of the thigh, which was definitely abnormal, although interpreted as posttraumatic. She also had both a central nervous system involvement in the form of loss of consciousness and abnormal MRI findings, and a peripheral neuropathy, confirmed by the nerve conduction study. In addition she had renal involvement with albuminuria and microscopic hematuria and a renal scar suggestive of infarction. There was no definite evidence of urinary tract infection.

Of note was a normal platelet count. The platelet count is of great interest in rheumatology because in most rheumatologic disorders with inflammation, thrombocytosis is commonly seen. A normal count suggests that there was no active inflammation at that time. ESR was borderline elevated and a detailed immunological panel was negative.

The following conditions should be considered in a patient with multisystem involvement: (1) infective endocarditis (2) systemic lupus erythematous (SLE) and (3) vasculitic syndromes.

Infective endocarditis. There is no setting for the patient to develop infective endocarditis but if this child had normal valve endocarditis, I cannot exclude it based on the data available.

SLE: From the physical findings, there is nothing to suggest SLE. Moreover, on two different occasions, both the antinuclear antibodies and the anti-double-stranded antibodies were negative. If ANA has been done by immunofluoresence and remained negative over a period of six months, I can with a fair amount of confidence rule out SLE.

Thus, I would like to rule out both these conditions, based on the data that has been provided.

Systemic vasculitis syndromes: These conditions can explain the multisystem involvement in this patient.

The common vasculitis disorders seen in children are classified into large vessel, medium vessel, and small vessel based on the vessel size(1,2). We shall discuss them one by one.

This is not the presentation of Takayasu disease since four limb pulses and blood pressure were normal. Temporal arteritis does not occur in children. Kawasaki disease: This diagnosis was excluded based on the clinical history and findings. Similarly there was no evidence of Henoch Schnolein Purpura, Wegener's granulomatosus, hypersensitivity angitis, urticarial vasculitis, and cryoglobulinemia related vasculitis.

Microscopic polyangitis and polyarteritis nodosa (PAN) are similar conditions that are included in the category of medium vessel vasculitis. PAN, first described by Kussmaul and Maier, was initially called periarteritis nodosa and described as a chronic, relapsing, febrile disease with protean manifestations resulting from inflammation of the small and medium-sized muscular arteries often leading to aneurysm formation. The hallmarks of the condition include.

(*i*) Non-specific signs and symptoms: Constitutional symptoms of fever and myalgias are frequent. PAN is one of the most difficult clinical diagnoses to make in children, and has a variable clinical course as can be expected from a disorder with diffuse vasculitis.

(*ii*) The clinical presentation depends on the system involved. The organ system involvement is episodic and unpredictable, just as in this patient. The childhood form of the disease is different from that described in adults. Ozen et al have described major and minor criteria for diagnosing childhood PAN. These criteria are guidelines for diagnosis of the disease based on experience at that center on 31 patients over 28 years. The major criteria pertain to renal and musculoskeletal involvement. Minor criteria, focus on cutaneous findings, peripheral neuropathy, hypertension, lung disease, increased acute phase reactants, gastrointestinal involvement, neurological and cardiac disease, constitutional symptoms, and presence of hepatitis B surface antigen(3).

A patient is said to have PAN if there are three criteria, including at least one major criterion. It is emphasized that these criteria have not been validated. The index case had the following features: renal disease, significant musculoskeletal involvement, cutaneous findings, peripheral neuropathy and neurological disease. However, she did not have constitutional symptoms, or hypertension which is seen in many patients with PAN. But a normal blood pressure in this patient can be explained as the variant of microscopic polyangiitis which does not have hypertension. The present patient definitely fulfills Ozen's criteria for PAN.

An important concern regarding the diagnosis of PAN in this patient includes the absence of fever. In our series on PAN, all the patients had fever. Most patients also show significant hypertension. More than 90% of our patients were hypertensive and most had elevated acute phase reactants(4).In fact, it is the hypertension which often points to the disease in addition to elevated acute phase reactants. It is therefore difficult to explain these findings in the context of a diagnosis of PAN. There is a subset of patients with polyarteritis that have mononeuritis multiplex. These children may have little or no systemic features. So, in our patient since there was a very prominent component of mononeuritis multiplex, even if this child did not have fever and hypertension, it could still be PAN.

Thus the chief clinical, laboratory and imaging findings are consistent with the diagnosis of PAN. This is a disorder that is known to be both episodic and steroid responsive as was the case in this patient. The skin rash though not typical of PAN is significant. Limb pain can be a very prominent finding in children because of neuropathy and muscle ischemia. Muscle disease can be explained as well. Increased CPK level, though not a very prominent feature can occur in PAN. The patient had classical mononeuritis multiplex. The neurological disease, loss of consciousness and MRI findings were all compatible with the diagnosis of PAN. The renal involvement, albuminuria, microscopic hematuria, are all present in patients with the microscopic polyangiitis, a variant of PAN.

There are two aspects of the case which are not well explained. These include the history of urinary infection and the renal scar. In the literature, there are case reports of abnormal intravenous pyelograms in patients with PAN. Here, the passage of the urine through the ureter is affected because the vascular supply to the ureter is compromised. Thus, infection could be a result of ureteral dysfunction and scars have been described in patients with PAN and ureteric dysfunction. However, if this patient had an otherwise unrelated urinary tract infection, then repeated episodes of urinary tract infection can result in scars as a result of reflux nephropathy(5,6). Thus, virtually all the problems described can be related to the main diagnosis of PAN.

Based on the history and the physical findings, the only differential diagnosis here is PAN. The diagnostic investigation which was done in the child was probably an angiography to confirm the diagnosis. The angiography would have shown micro aneurysms and may be arterial narrowing beyond that. Another procedure that would have been helpful was a muscle biopsy from the sites which were shown to be abnormal on MRI. The muscle biopsy would have shown evidence of vasculitis. Thus, muscle biopsy could also have been done but a more definitive investigation would have been some form of the angiography, either an MR angiography or a conventional angiography.

Similar clinical features may be seen in patients with infection associated vasculitis. We have managed one such patient who was admitted with the diagnosis of microscopic polyangiitis, had all the typical features of microscopic polyangiitis including glomerular nephritis and was found to have antibodies against parvovirus B19. This child recovered on her own and remains well(7). Thus, parvovirus B19 may have a very similar presentation and it can mimic all the features of systemic vasculitis. We have also seen a patient with varicella glomerulonephritis, an uncommon complication(8), while as a group, infection- associated vasculitis(9) can be considered as a differential diagnosis, the most likely diagnosis in this case is PAN.

Dr Arvind Taneja (Pediatrician) The urine infection discussed may be a red herring because one urine culture showing insignificant growth does not

confirm the diagnosis of urinary infection. Contamination due to improper collection is a possibility.

Dr Singh I agree, it would be important only if the child had been on antibiotics.

Dr Sawhney This young child came to me after she had a cerebral MRI which suggested vasculitis. On review of the history, clinical examination and detailed investigations, two things were clear. Firstly, she was episodically unwell and well enough between times to attend school. Thus, this was not the clinical gestalt of a patient with severe systemic vasculitis or frank connective tissue disease. It appeared more like an embolic phenomenon. Secondly her inflammatory parameters were not raised. This raised the question that the child had a "vasculitic mimic". The diagnostic investigation that clinched the diagnosis was an echocardiogram.

Dr Buxi (Radiologist) I will briefly discuss the imaging. The MRI done showed multiple areas of cortical altered signal intensity in the kidney. The gluteus maximus and the right rectus femoris muscles have features suggestive of inflammation (***Fig.* 2**). In the brain, T2 weighted axial image revealed multiple small hyperintense areas in the vicinity of the left caudate, left frontal periventricular region and the left lenticular region. Small hyperintense lesion was seen in the right basal ganglion as well. These findings are suggestive of multiple infarcts (***Figs.* 3*a*** and **3*b***). The possibility of an embolic phenomenon affecting the skin, muscles, kidney and brain should be considered.

Dr Mohanty (Cardiologist) On clinical examination the cardiovascular system was normal. On echocardiogram the left atrium was slightly enlarged and there was a solitary mass measuring 3 cm x 3 cm attached to lateral wall of the left atrium. It was just prolapsing into the left ventricular cavity during systole. There were no areas of necrosis or haemorrhage and a clinical diagnosis of left atrial myxoma was made (***Fig.* 4**).

Dr Sujata Sawhney The cardiology team opined that the myxoma was prolapsing into the left ventricle during systole. The patient was at risk of obstructive cardiac failure and hence underwent cardiac surgery within twelve hours of diagnosis.

Dr G Shivnani (Cardiac Surgeon) The patient was put on a cardiopulmonary bypass and a large pedunclated mass 3 cm x 3 cm was found attached to the lateral wall of the left atrium, just inferior to right superior pulmonary vein. The mass was excised and the child had an uneventful recovery.

Dr Subimal Roy (Pathology) The specimen consisted of multiple polypoidal and mucoid grey pink pieces of tissue, measuring 4 × 3 × 2 cm. In one fragment a pedicle was identified which was 0.5 cm long. Microscopic examination showed polypoid tissue covered with flattened endothelial cells. The stroma showed marked myxoid change with focal hemorrhages, many small capillaries and a diffuse inflammatory infiltrate of lymphocytes, plasma cells and occasional polymorphs (***Fig.* 5**).The findings were compatible with the diagnosis of atrial myxoma.

LITERATURE REVIEW

More than 50% of primary tumors in the heart are cardiac myxomas. A review of 1029 patients showed that 83.0% of myxomas were located in the left atrium and 12.7% in the right atrium(10). About 15% patients may be asymptomatic for a long period of time. When they are symptomatic, majority of patients with myxomas may experience symptoms due to central or peripheral embolism or intracardiac obstruction. Claudication is also well reported(11). If

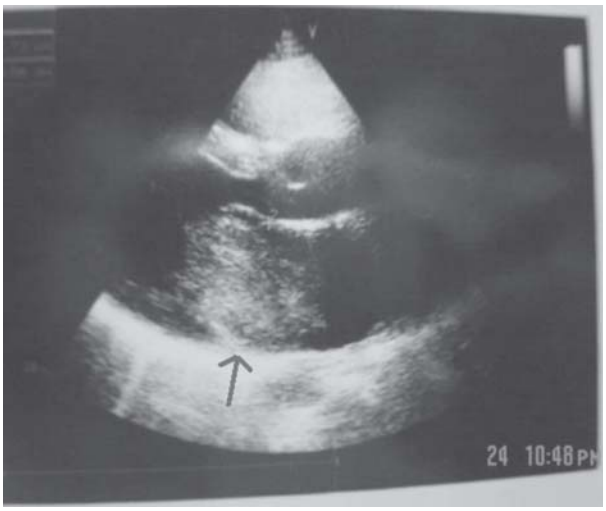

FIG. 4 *LA myxoma on echocardiography showing a solitary mass measuring 3x3cm attached the lateral wall of the left ventricle.*

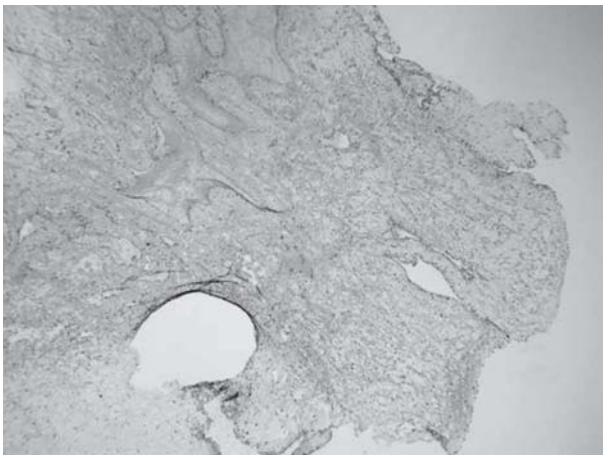

FIG. 5 *Low power view of myxoma shows polypoidal tissue covered with flattened endothelial cells. Stroma shows myxoid change with inflammatory cell infiltrate.*

the tumor is in the right heart chambers it may cause pulmonary emboli, a Budd-Chiari syndrome and remittent or lasting fever. Weight loss, chronic anemia, arthralgia, polycythemia and hypergammaglobinemia may occur in some patients. These manifestations often disappear after resection of the tumor(10).

Generally most of the cases of atrial myxoma are sporadic (90%). A small numbers of cases are familial as in Carney syndrome. The condition is characterised by a complex of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas. It is a multiple endocrine neoplasia (MEN) and lentiginosis syndrome that is inherited in an autosomal dominant manner and is genetically heterogeneous(12). Although myxomas are most common in left atrium, they can occur in the right side or even be multiple. The index patient is a case of nonfamilial cardiac myxoma which is generally solitary.

Final diagnosis: *Left atrial myxoma*

Dr Sawhney There are 107 cases of atrial myxomas reported till 2004, both in adults and children. The female-male ratio is 3:1. The mean age is 43 years and of note, more than 80% of the patients were detected after a stroke and one-fourth of them are autopsy reports(13). The first antemortem report of left atrial myxoma was in a 3-yr-old child who was diagnosed to have the myxoma when he presented with recurrent hemiplegia. The same paper reviewed nine children, of these 8 had a stroke prior to diagnosis, 6 had erythematous rashes on the extremities, 4 had normal cardiac examination and two had a recurrence(14).

Dr Singh How are the skin rashes, lack of cardiac findings and the neurological features explained?

Dr Sawhney On literature review of nine children, vast majority had rashes. The reason for the transient cutaneous eruptions involving the extremities was most likely attributable to fragmentation of the atrial tumor with peripheral embolization. Several patients may have no clinical symptoms or signs referable to the cardiovascular system(14).

Dr Manvir Bhatia (Neurophysiologist) The NCV done at this centre showed that the left sural nerve was definitely delayed in latency, had a decreased amplitude and conduction velocity. This was the same leg where she had developed numbness. I think that possibly was a vascular phenomenon which involved the sural nerve. Involvement of a single sensory nerve does not fit the criteria for mononeuritis multiplex. Study of the left median nerve revealed decreased amplitude only, with no change in latency and conduction velocity. This is not suggestive of a neuropathy involving the median nerve.

Dr Singh The response to steroids: how is this explained?

Dr Sawhney I think this was incidental. The child had episodic phenomenon of embolization and was well between the episodes.

The patient continues to be on regular follow up. Multiple follow up echocardiograms are normal and she remains well. Since a small percentage of patients may have a recurrence, patients need careful follow up. The present case suggests that atrial myxoma should be considered in the differential diagnosis when children present with unexplained neurologic symptoms or with signs of embolization, because surgical removal of the tumor is curative(14).

Funding: None.

Competing interests: None stated.

REFERENCES

1. Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, *et al*. EULAR/Press endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis 2006; 65: 936-941.
2. Ozen S. The spectrum of vasculitis in children. Best Pract Res Clin Rheumatol 2002; 16: 411-425.
3. Ozen S, Besbas N, Saatci U, Bakkaloglu A. Diagnostic criteria for polyarteritis nodosa in childhood. J Pediatr 1992; 120: 206-209.
4. Kumar L, Sarkar B, Singh S, Bajwa RP, Joshi K, Malik N. Polyarteritis nodosa—a few unusual findings. Indian Pediatr 1996; 33: 459-464.
5. Kaskarelis IS, Zarifi M, Dantis P, Vrachliotis G. Bilateral ureteral involvement in polyarteritis nodosa. Scand J Urol Nephrol 1995; 29: 323-326.
6. Melin JP, Lemaire P, Birembaut P, Aubert L, Cohen J, Lardennois B, *et al*. Polyarteritis nodosa with bilateral ureteric involvement. Nephron 1982; 32: 87-89.
7. Dass R, Ramesh P, Ratho RK, Saxena AK, Singh S. Parvovirus B19-induced multisystem disease simulating systemic vasculitis in a young child. Rheumatol Int 2005; 25: 125-129.
8. Dass R, Singh S, Kumar V, Vaiphei K, Agrawal S, Saeed T, *et al*. Varicella glomerulonephritis mimicking microscopic polyangiitis. Rheumatol Int 2004; 24: 362-364.
9. Pagnoux C, Cohen P, Guillevin L. Pagnoux C, Cohen P, Guillevin L. Vasculitides secondary to infections. Clin Exp Rheumatol 2006; 24: S71-81.
10. Kuon E, Kreplin M, Weiss W, Dahm JB. The challenge presented by right atrial myxoma. Herz 2004; 29: 702-709.
11. Gavrielatos G, Letsas KP, Pappas LK, Dedeilias P, Sioras E, Kardaras F. Large left atrial myxoma presented as fever of unknown origin: a challenging diagnosis and a review of the literature. Cardiovasc Pathol 2007; 16: 365-367.
12. Malchoff CD. Editorial: Carney complex—clarity and complexity. J Clin Endocrinol Metab 2000; 85: 4359-4366.
13. Ekinci EI, Donnan GA. Neurological manifestations of cardiac myxoma: a review of the literature and report of cases. Intern Med J 2004; 243-249.
14. Al-Mateen M, Hood M, Trippel D, Insalaco SJ, Otto RK, Vitikainen KJ. Cerebral embolism from atrial myxoma in pediatric patients. Pediatrics 2003; 112: 162-167.