We report a 3-year-old girl with Kawasaki disease who presented with retropharyngeal edema and shock syndrome. This is the first reported case in Taiwan. The patient initially presented with fever, cough, and pyuria followed by rapidly progressive enlarged bilateral cervical lymphadenopathy. On the third day of the fever, computed tomography for airway compression sign found widening of the retropharyngeal space mimicking a retropharyngeal abscess. Later, an endotracheal tube was inserted for respiratory distress. A skin rash over her trunk was also noted. On the fifth day of the fever, the clinical course progressed to hypotension and shock syndrome. Because of more swelling of bilateral neck lymph nodes, computed tomography was arranged again and revealed partial resolution of the edematous changes in the retropharyngeal space. Edema of the hands and feet, bilateral bulbar conjunctivitis, and fissured lips were subsequently found. The diagnosis of Kawasaki disease was confirmed on the eighth day of fever. There was no evidence of bacterial infection. She was administered intravenous immunoglobulin (2 mg/kg) and high dose aspirin (100 mg/kg/day). One day later, the fever subsided, and her blood pressure gradually became stable. Heart echocardiography on the Day 13 revealed dilated left coronary artery and mitral regurgitation. Follow-up echocardiography six months later showed normal coronary arteries. To date, the patient has not experienced any complications. This case illustrates that retropharyngeal edema and shock syndrome can be present in the same clinical course of Kawasaki disease. Clinicians and those who work in intensive care units should be aware of unusual presentations of Kawasaki disease to decrease rates of cardiovascular complications.

* Corresponding author. Department of Pediatrics, Mackay Memorial Hospital, 92 Chungshan North Road, Section 2, Taipei 104, Taiwan. E-mail address: abc4540@gmail.com (S.-D. Shyur).

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Kawasaki disease (KD), also known as acute febrile mucocutaneous lymph node syndrome, was first described in the Japanese literature by Dr Tomisaku Kawasaki in 1967, and in the English literature in 1974. This disease is a systemic vasculitis involving all blood vessels, but predominantly medium-sized arteries and is one of the most common vasculitides of childhood. However, it may cause severe complications, morbidity, and even mortality if not appropriately treated. Eighty-five percent of affected patients are younger than 5 years old, and it is more common in boys than in girls (male to female ratio, 1.36:1 to 1.62:1). It occurs worldwide in all ethnic groups, and Asian populations have a higher risk than other ethnic groups.

Typically, KD can be diagnosed by fever persisting for at least 5 days, and the presence of at least four of the following principal features: (1) changes in the extremities; (2) polymorphous exanthema; (3) bilateral bulbar conjunctival injection without exudates; (4) changes in the lips and oral cavity; and (5) cervical lymphadenopathy (>1.5 cm diameter). Exclusion of other diseases with similar symptoms is also necessary.

Because of the systemic involvement, it has high variability in all organ systems, and early diagnosis in patients with atypical KD or in those with uncommon manifestations is difficult. With the widespread use of computed tomography (CT), there is an increasing number of reports of KD with retropharyngeal edema and enlarged lymph nodes (the left was largest at: 2.5 × 3 cm) along bilateral internal jugular veins, from the submandibular triangle to the level of cricoid cartilage. Due to the suspicion of a retropharyngeal abscess, surgical exploration was performed with open drainage for tissue proof. Intubation with mechanical ventilation was used after the operation to relieve the airway compression and was kept for persisted enlarged lymph nodes of the neck.

In this paper, we review the literature and report the case of a Taiwanese child with KD who had retropharyngeal edema and shock syndrome.

Case report

A 3-year-old girl presented with cough for 2 weeks and fever up to 40°C for 2 days. Physical examination found injected throat, coarse breath sounds with no palpable lymph nodes, no audible heart murmur, and no skin rash. Initial laboratory data revealed pyuria, white blood cell count of 39.6 × 10^9/L, and an elevated CRP level of 197 mg/L. Empiric antibiotics with ampicillin and gentamicin were prescribed; however, she had bilateral progressive swelling of the lymph nodes in her neck on the following day. On the third day of the fever, in addition to her progressive neck swelling (Fig. 1A in comparison to Fig. 1B, her usual appearance), she had torticollis, respiratory distress, and a skin rash over her trunk. A lateral view X-ray of the neck found retropharyngeal space widening. CT was performed to localize the lesion causing airway compression, and showed retropharyngeal edema, a suspected retropharyngeal abscess, and enlarged lymph nodes along bilateral internal jugular veins. Due to the suspicion of a retropharyngeal abscess, surgical exploration was performed with open drainage for tissue proof. Intubation with mechanical ventilation was used after the operation to relieve the airway compression and was kept for persisted enlarged lymph nodes of the neck.

On the fifth day of the fever, tachycardia and hypotension (77/36 mmHg), cooling of extremities, and oliguria (0.47 ml/kg/h) were noted. After fluid resuscitation with normal saline (20 ml/kg), inotropic agents were given for sustained hypotension and shock syndrome. Due to the suspicion of a retropharyngeal abscess, surgical exploration was performed with open drainage for tissue proof. Intubation with mechanical ventilation was used after the operation to relieve the airway compression and was kept for persisted enlarged lymph nodes of the neck.

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Figure 1. (A) On the third day of the illness, the patient had torticollis, respiratory distress and bilateral progressive swelling lymph nodes in her neck. (B) Patient’s usual appearance before the illness.
thromboplastin time 32.9 seconds, albumin 23 g/L, Na 137 mEq/L, aspartate aminotransferase 270 IU/L, and alanine aminotransferase 159 IU/L. The antibiotics were shifted to vancomycin, cefotaxime, and metronidazole for suspected septic shock. Checks were also made for rheumatoid factor, antinuclear factor, and Epstein-Barr virus profile and ASLO (Anti-streptolysin O) titer, but they were all negative. CT was performed again for the bilateral progressive swelling of the lymph nodes in her neck and the suspicion of the extension to the thoracic cavity. The results showed partial resolution of the edematous changes involving the retropharyngeal soft tissue, and more swelling of the lymph nodes (left increased to 3 × 3 cm) along the bilateral internal jugular veins from level II to IV (Fig. 2C). The culture of aspirated fluid from the pharynx and throat grew normal flora. Cultures from her blood, urine, and throat swab also revealed no growth. On the seventh day of the fever, physical examination found edema of the hands and feet, bilateral bulbar conjunctivitis, and desquamation over the perianal area. The next day, fissured lips were

Figure 2. (A) Sagittal view of a computed tomography scan on the third day showing a hypodense lesion (about 1 × 4 cm) without ring enhancement over the retropharyngeal space from the skull base to the bony level of C7. A retropharyngeal abscess was suspected. (B) Axial view of a computed tomography scan on the third day showing a hypodense lesion (about 1.8 × 3 cm) without ring enhancement over the retropharyngeal space. (C) Repeat sagittal view of computed tomography scan 2 days later, showing partial resolution of the edematous change involving the retropharyngeal soft tissue, the nasopharyngeal and oropharyngeal walls.
Kawasaki disease with retropharyngeal edema and shock

also noted. Although M-mode and 2-dimensional echocardiography showed normal right coronary artery (RCA; 0.185 cm) and left coronary artery (LCA; 0.201 cm) at that time, Kawasaki disease was diagnosed. She was adminis-
tered intravenous immunoglobulin (IVIG; 2 mg/kg) and aspirin (100 mg/kg/day) on the eighth day of the fever. One day later, the fever subsided and her blood pressure gradu-
ally became stable. Inotropic agents including dopamine and epinephrine were tapered within 1 day. The endotra-
cheal tube was removed and the antibiotics were dis-
continued the next day. Follow-up heart echocardiography on the thirteenth day found a normal RCA (0.243 cm), dilated LCA (0.372 cm), and mitral valve regurgitation. Finally, the fever persisted for 9 days. She was discharged without other complications. She took low dose aspirin (5 mg/kg/day) for a further 6 months. Follow-up heart echocardiography 6 months after she had been discharged showed that the dilated LCA had become normal (0.251 cm), and the mitral valve was without regurgitation.

Discussion

The incidence of KD is highest in Japan, with more than 186,000 cases being registered since 1967, and an average annual incidence rate of 184.6 per 100,000 children aged 0 to 4 years. In Taiwan, one study reported that 3877 children and adolescents aged <20 years were hospitalized for KD between 2003 and 2006. Ninety percent of these children were aged <5 years, with a male to female ratio of 1.62:1 and overall incidence of 69 per 100,000 children. Taiwan has the third highest incidence of KD in the world, after Japan and Korea. In Taiwan, it occurs more frequently during the summer.

The signs and symptoms of KD are due to a systemic necrotizing vasculitis with fibrinoid necrosis of the medium-sized muscular arteries, and the coronary arteries are the predominant sites of involvement.

Our patient had retropharyngeal edema and shock. The precise pathophysiology of the association of KD with retropharyngeal pathology is unclear. However, inflammation and edema were considered the main mechanism. Increased microvascular permeability is an initial step of KD, and vascular endothelial growth factor might play a role in the vascular leakage. Increases in vascular leakage cause hypoalbuminemia and noncardiogenic edema. Because the retropharyngeal space consists of loose connective tissue, local edema could preferentially develop in the space under the generalized inflammatory condition, when deep neck lymphadenopathy is present. One study reported 6 Japanese KD patients showing retropharyngeal low-density areas on CT. Transient hyponatremia (<135 mEq/L) and hypo-
albuminemia (<30 g/L) were observed in five and four patients, respectively. Our patient had hypoalbuminemia (albumin 23 g/L) but no hyponatremia (Na 137 mEq/L).

Hypotension in patients with KD is likely to be multi-
factorial, and possible explanations include vasculitis with ongoing capillary leak, myocardial dysfunction, and cyto-
kine dysregulation. Inflammatory cytokines are known to damage myocardial cells and work as cardiac depressants. In animal models, tumor necrosis factor-α and interleukin-6 have been reported to cause myocardial depression.

Cardiogenic shock in KD could be caused by arrhythmia, ischemic heart disease, valvular disease, endocarditis, and myocarditis, but these complications were ruled out by echocardiography and electrocardiography. The echocardiography of our patient revealed normal ejection fraction of the left ventricle (0.655), LCA dilatation and mitral regurgitation. Therefore, the possibility of cardio-
genic shock in our patient was low. We supposed that dys-
regulated vasomotor tone and reduced vascular resistance has a greater contribution to shock.

One hypothesis is that a ubiquitous childhood infectious agent causes KD, and that symptomatic illness occurs only in genetically predisposed persons. However, the exact genetic factors that may cause the disease are unknown. Our patient was a Taiwanese girl, and some studies have reported an association of inositol 1,4,5-trisphosphate 3-
kine C (ITPKC) gene single nucleotide polymorphism rs28493229 with Kawasaki disease susceptibility in the Taiwanese population. In addition, one study indicated that Taiwanese patients with KD carrying the ITPKC rs28493229 C allele had a significantly higher risk of aneu-
rysms formation.

Head and neck manifestations of KD show high variability, and unusual presentations may lead to a delayed diagnosis. Presentations that have been reported include mastoiditis, cervical adenitis, upper airway obstruction, pharyngitis, acute tonsillitis, torticolis, retropharyngeal abscess-like, parapharyngeal abscess, and peritonsillar abscess.

Cervical lymphadenopathy is the least common mani-
festation, occurring in 50% to 75% of patients. However, cervical lymphadenopathy may precede all other symptoms, particularly in atypical cases. The rate of cervical lymphadenopathy occurring as the initial presenting symptoms is only approximately 12%. In our patient, cervical lymphadenopathy appeared as the first presentation. Lymphadenopathy is usually unilateral and may appear to involve only one single node. One report mentioned six KD patients with retropharyngeal changes and cervical or deep neck lymphadenopathy. Those swelling lymph nodes may locate in one side or bilaterally. The enlarged lymph nodes of our patient were bilateral and include several nodes.

The true incidence of retropharyngeal pathology in KD is unknown. There are some reports of patients with KD who underwent surgical exploration in retropharyngeal areas, but cultures of the inflammatory material were sterile in all cases. To date, no study has reported KD accompanied with a proven retropharyngeal abscess. Therefore, we hypothesize that the retropharyngeal space widening and edematous change were presentations of inflammation in KD. One study compared 56 cases with retropharyngeal low density (RLD) on CT diagnosis. The author divided these patients into two groups; Group A included 34 patients diagnosed as KD and Group B included 22 patients diagnosed as non-KD. Group A had greater thickness of RLD, greater scores of the RLD extent into the deep neck spaces, greater scores of the adjacent soft tissue changes than Group B. Therefore, KD patients with retropharyngeal space changes have stronger inflammatory reactions than non-KD patients.

Approximately 20% of KD patients will develop cardio-
vascular manifestations during the course of their disease.
Cardiovascular manifestations include pericarditis, myocarditis, aortic root dilatation, valvulitis, coronary artery lesions such as dilatation, aneurysm and/or stenosis. Some severely affected patients even die suddenly. The major complication of KD is coronary artery aneurysms, which develop in 25% of untreated patients making KD the leading cause of acquired heart disease among children in the developed world. Therefore, early diagnosis of this disease and avoiding cardiovascular complications are important for clinicians.

Shock is an uncommon presentation of KD. Two studies reported incidences of shock in KD patients of 2.4% and 7%. In Dominguez et al’s study, the percentage of KD patients admitted to the intensive care unit (ICU) ranged from 0% to 10%. One study found that shock and hypotension requiring critical care support occurred with increasing frequency in patients with acute KD. Kanegaye et al discussed “Kawasaki disease shock syndrome” and defined it on the basis of systolic hypotension for age, a sustained decrease in systolic blood pressure from baseline of ≥20%, or clinical signs of poor perfusion. Our patient fulfilled these criteria. She had persistent hypotension requiring inotropic agents support and poor perfusion sign. Kanegaye et al found that KD with shock was more common in females or clinical laboratory data with larger proportions of band counts, higher C-reactive protein concentrations, lower hemoglobin concentrations and platelet counts, and evidence of consumptive coagulopathy, which is consistent with the clinical condition of our patient. We assume that our patient had a more intense inflammation reaction than other patients with KD without shock.

Both retropharyngeal involvement and shock syndrome carried higher risk for cardiac involvement. According to one study, 11 reported cases of KD presented initially as retropharyngeal suppurrative disease. Echocardiography demonstrated one patient with pericardial effusion, three with coronary artery dilatation or ectasia, and three with coronary artery aneurysm. In that study, KD patients with retropharyngeal involvement have higher risk of cardiovascular complications. Patients with KD and shock have also been reported to have higher incidences of coronary artery abnormalities, mitral regurgitation, and prolonged myocardial dysfunction. In one study, among 13 patients with KD shock syndrome, 46% (6 of 13) had coronary artery dilatation, and 15% (2 of 13) had coronary artery aneurysms. In another study, among 14 patients with KD admitted to the ICU, 43% (6 of 14) of the patients had coronary artery abnormalities.

Other less common clinical findings of KD include arthritis, diarrhea, intestinal hemorrhage, hepatic dysfunction, hydrops of the gallbladder, aseptic meningitis, seizure, and urethritis. Our patient had diarrhea, hepatic dysfunction, splenomegaly, and pyuria.

The differential diagnosis of KD should include viral illness, bacterial infection, immune reactions, Steven-Johnson syndrome, rheumatic disease, and systemic-onset juvenile idiopathic arthritis. In our patient, the differential diagnosis included poststreptococcal scarlet fever, toxic shock syndrome, Epstein-Barr virus or adenovirus virus infection, drug hypersensitivity reaction, and other rheumatic disease. However, the ocular, mucosal and extremity changes in our patient led us to the diagnosis of KD.

Most KD patients are initially treated with intravenous antibiotics, and those admitted to the ICU are often treated for septic shock or toxic shock. However, the clinical course will still progress, and the diagnosis may be delayed for more than 10 days. The American Academy of Pediatrics and the AHA recommend that children with KD should be treated with aspirin and IVIG during the first 10 days of the illness. IVIG is most effective in reducing the risk of coronary artery disease when administered within 10 days of the onset of fever. Our patient was found to have coronary artery dilatation on the thirteenth day of the illness, even though IVIG and aspirin had been given on the eighth day. Although standard therapy with IVIG and aspirin given within the first 10 days of illness greatly improves outcomes, approximately 5% of children still develop coronary artery aneurysms.

Fever has been shown to return within 48 hours after treatment with IVIG in 10% to 20% of children. Refractory KD may require repeat immunoglobulin, immunosuppres- sant, steroid, or plasma exchange treatment. Patients with KD and shock seem to have higher incidences of IVIG resistance, and require additional anti-inflammatory treatment. Our patient was fortunate and had a good response to the first dose of IVIG.

Surgical exploration was helpful in the differential diagnosis of our patient. However, if we had had more experience of the natural course of KD with retropharyngeal edema, we could have avoided this unnecessary surgical intervention.

The present mortality rate of KD is low. In Japan, mortality rates are about 0.01%, and overall, 50% of coronary artery aneurysms resolve 1 to 2 years after the illness. Because there are only a few studies on patients with KD with retropharyngeal edema or shock, the long term-prognosis is not clear. Although our patient had left coronary artery dilatation and mitral valve regurgitation on the thirteenth day of the illness, they were shown to have resolved on echocardiography 6 months later.

The clinical diversities of KD increase the difficulty of diagnosis. Clinicians should be alert to head and neck manifestations that show a poor response to initial intravenous antibiotics, as they could be early presentations of KD. Unusual manifestations of KD could initially present as torticollis, lymphadenopathy, deep neck infection or shock syndrome, prior to those typical mucosal and skin changes. Clinicians should be more alert to KD, and then earlier immunoglobulin usage may decrease the risk of complications, especially cardiovascular abnormalities such as coronary artery dilatation or stenosis, shock, and even death.

Conflicts of interest

All authors declare that they have no conflicts of interest related to the material discussed in this article.

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