Rethinking the Typical Diagnostic and Therapeutic Challenges of Kawasaki Disease

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Keywords

Kawasaki disease · Retropharyngeal abscess · Deep neck abscess · Refractory Kawasaki disease · Intravenous immunoglobulin resistance · Acquired clotting inhibitor

Abstract

This report presents a case of a 9-month-old male subject, with an initial presentation of a viral-like illness progressing rapidly to multiple deep neck abscesses involving the bilateral submandibular, parapharyngeal, retropharyngeal, and anterior mediastinal spaces subsequently confirmed with contrast-enhanced computed tomography of the neck. Additionally, the subject developed mucocutaneous signs of generalized erythematous rash, with red, fissured lips along with edema of the extremities. Initial lab parameters were suggestive of high inflammatory markers, low albumin, and deranged coagulation profile. Treatment with broad-spectrum intravenous antibiotics, albumin, and fresh frozen plasma infusions was commenced. Echocardiography revealed dilatation of the left main coronary artery with mild mitral valvular regurgitation. Based on the clinical criteria, a diagnosis of typical Kawasaki disease (KD) on day 5 of illness was

made, and the subject received intravenous immunoglobulin (IVIg) and aspirin. The clinical course was complicated by IVIg resistance, for which a second dose of IVIg and pulse systemic corticosteroid therapy was required. Post defervescence, an isolated elevation of activated thromboplastin time, partially corrected with mixing studies and a positive circulating lupus anticoagulant was noted. The patient did not develop any bleeding or thromboembolic complications during his hospital stay. Surgical drainage of the neck abscesses did not yield any pus or fluid collection. After a stormy course of 31 days, the subject was discharged with an improving trend of inflammatory markers and no progression of coronary artery dilatation. Gradual resolution to baseline health was noted upon follow-up, 18 months post-discharge from the hospital. Despite being one of the most common cause of childhood acquired cardiac disease, KD still poses a significant diagnostic and treatment challenge to physicians. This requires physicians to be vigilant for timely diagnosis and appropriate management to prevent significant cardiac comorbidities and be aware of the possible complications that might arise during the treatment.

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Introduction

Kawasaki disease (KD), synonymized as acute febrile mucocutaneous syndrome, was first identified by the Japanese physician Dr. Tomisaku Kawasaki in 1967 [1]. It is described as an acute systemic vasculitis of unknown etiology involving the medium-sized blood vessels. Presence of fever for five or more days combined with the presence of four of the five clinical features of polymorphous rash, unilateral cervical lymphadenopathy, oral lips and mucosal changes, non-purulent conjunctivitis, and changes of extremities are the diagnostic criteria for typical KD [2]. Of these symptoms, the most infrequent symptom is cervical lymphadenopathy (50%–75%), while the others occur in 90% of the cases [3]. Cervical lymphadenopathy as the initial presenting symptom occurs only 12% of the time [4], and cases of retropharyngeal abscesses presenting as KD is even more uncommon [5], leading to potential misdiagnosis and treatment delays.

The timely diagnosis and treatment of KD with intravenous immunoglobulin (IVIg) are cardinal in preventing cardiac complications, predominantly coronary artery abnormalities [2]. However, approximately 10–20% of KD patients are considered resistant to IVIg and hence are at an increased risk of coronary artery abnormalities [6, 7].

Atypical presentation combined with IVIg resistance compounds the challenges faced in diagnosing and effectively treating KD to improve health outcomes and prevent long-term morbidity. Here, we present the case of a child with an eventual diagnosis of IVIg-resistant KD who presented in a tertiary care hospital in Dubai, the United Arab Emirates, with an acute febrile illness followed by bilateral cervical lymphadenitis rapidly progressing to bilateral deep neck and upper mediastinal abscesses.

Case Presentation

A 9-month-old, previously healthy Arab boy with an unremarkable anamnesis presented to our emergency department with a 1-day history of fever, non-bilious vomiting, and loose stools. On admission, his clinical examination was positive for fever with a tympanic temperature of 38.5°C, dry mucus membranes, small erythematous papules over the cheeks, and non-tender hepatomegaly of 4 cm below the right costal margin. His vital parameters and other systemic examination were within normal limits.

According to the National Vaccination Schedule, his immunization status was up-to-date, and he was developmentally appropriate for his age. Furthermore, his family and socioenvironmental history were unremarkable.

Initial investigations revealed neutrophilic leukocytosis (WBC: 18,900/ μ L, ANC: 17,300/ μ L, and ALC: 800/ μ L), mild microcytic, hypochromic anemia (Hgb: 9 g/dL, MCV: 71.9 fL, and MCH: 23.2 pg), and normal platelet counts (22,700/ μ L). His urea and electrolytes were within normal limits, stool analyses were normal with no viruses detected, and stool culture was subsequently reported as sterile.

He was admitted to the pediatric ward as a case of acute viral gastroenteritis and started on intravenous (IV) fluids, antipyretics, and supportive measures. Over the next 48 h, he developed rapidly increasing right-sided neck swelling, 4 × 2 cm, extending across the midline, redness of the overlying skin, hoarseness of voice, and bilateral periorbital edema. IV antibiotics (IV ceftriaxone at 100 mg/kg/day and IV flucloxacillin 100 mg/kg/day) were initiated. Further investigations revealed raised inflammatory markers (C-reactive protein: 391.1 mg/L, procalcitonin: 9.25 ng/mL). Liver function tests depicted mildly elevated serum glutamic-pyruvic transaminase (43 U/L) and total bilirubin levels (1.2 mg/dL) and low albumin (2.4 g/dL) with normal total protein and globulin levels. Virology screening, including the Epstein Barr virus, cytomegalovirus, and respiratory viral panel, was negative. The coagulation profile was deranged with prothrombin time of 17.5 s, activated partial thromboplastin time (APTT) of 56.7 s, and an international normalized ratio of 1.46. He also had sterile pyuria (WBC 10–15 cells/HPF). Ultrasonography of the neck revealed diffuse bilateral cellulitis with bilaterally enlarged cervical lymph nodes.

Given extensive and rapidly progressive cervical cellulitis, otolaryngology and maxillofacial surgery consults were made, and he was transferred to the pediatric intensive care unit for close monitoring for possible airway compromise. IV clindamycin (30 mg/kg/day) was added to the treatment regime, and an infusion of fresh frozen plasma (10 mL/kg) and 20% albumin (1 g/kg) was initiated given the derangement of the coagulation profile and hypalbuminemia, respectively.

On day 4 of hospital admission (day 5 of fever onset), he developed a new-onset generalized erythematous rash with cracked lips and edematous hands and increasing bilateral cervical swelling. Hence, the clinical diagnosis of typical KD was made. Echocardiography (ECHO) revealed dilatation of the left main coronary artery (3.5 mm, Z-score: +3.3) and mild mitral valve regurgitation with good cardiac function. Given progressive neck swelling, the endotracheal tube was electively placed, and in view of clinical and ECHO findings, he received the first dose of IVIg at 2 g/kg over 12 h along with an anti-inflammatory dose of aspirin (30 mg/kg/day).

Following the first IVIg infusion, his inflammatory markers showed a downward trend with normalization of the coagulation profile (Table 1), and body cultures (blood, urine, and stool) remained sterile throughout. Nevertheless, he continued to spike fever post 48 h of IVIg infusion with no change in the size of the neck swelling, and hence he was diagnosed as IVIg-resistant KD and received a second dose of IVIg (2 g/kg).

However, the patient remained febrile, and hence on day 10 of admission, pulse systemic corticosteroid therapy with methylprednisolone (30 mg/kg/day) was initiated for 3 days. Echocardiography was repeated, and it showed persistent left main coronary artery ectasia without aneurysmal dilatation.

Subsequent to systemic steroids administration, his clinical condition improved, fever resolved, and C-reactive protein showed a declining trend. IV antibiotics were continued, and the aspirin dose was reduced to the anti-platelet dose of 3 mg/kg/day. However, there was no perceived change in the size of the neck swelling.

Table 1. Summary of the inpatient laboratory results

Component	Reference range	On admission	Pre-IVlg	Post-2 doses of IVlg	Post-steroids	Pre-discharge
Full blood count						
White cell count, 10 ³ /μL	6.0–18.0	18.9	19.2	10.9	6.5	13.6
Hemoglobin, g/dL	11.1–14.1	9.0	9.2	9.0	9.6	10.5
MCV, fL	72.0–84.0	71.9	72.9	78.8	79.4	82.1
Platelets, 10 ³ /μL	200–550	227.0	187.0	719.0	368.0	515.0
Absolute neutrophil count, 10 ³ /μL	1.0–6.0	17.3	11.7	5.9	1.8	2.5
Absolute lymphocyte count, 10 ³ /μL	3.5–11.0	0.8	2.7	4.3	3.6	9.9
Blood film	WBCs are normal in count, RBCs show mild anemia with normocytic normochromic morphology, no immature cells					
Liver function tests						
Total bilirubin, mg/dL	0–1.2	1.2	1.2	0.3	0.4	0.6
SGPT, μ/L	0–33	43.0	29.0	9.0	17.0	12.0
Albumin, g/dL	3.8–5	2.4	2.3	2.9	3.9	4.9
Electrolytes						
Sodium, mmol/L	131–145	133.0	133.0	140.0	138.0	136.0
Inflammatory markers						
CRP, mg/L	<5.0	–	391.1	33.3	27.8	3.2
PCT, ng/mL	<0.05	–	9.0	–	–	–
ESR, mm/1 h	0–20	–	–	67.0	82.0	50.0
Coagulation profile						
PT, s	10.0–11.4	–	17.5	13.4	14.1	14.4
INR	0.8–1.1	–	1.4	1.0	1.1	1.1
APTT, s	31–44	–	56.7	50.4	101.9	90.9
APTT MIX	28–40	–	–	–	70.7	66.8
Fibrinogen	82–383	–	443.0	–	378.0	–
Lupus anti-coagulant	Negative	–			Positive	
Histopathology of tissue biopsy	Right cervical lymph node excision biopsy Reactive lymphoid hyperplasia with marked perilymphadenitis No evidence of granuloma or malignancy is seen					
Immunohistochemistry marker in the histopathology						
CD68	Positive in the histocytes and foamy macrophages					
CD1a and Langerin	Negative for Langerhans cells histiocytosis					

SGPT, serum glutamic-pyruvic transaminase; CRP, C-reactive protein; PCT, procalcitonin; PT, prothrombin time; INR, international normalized ratio.

Contrast-enhanced computed tomography (CT) of the neck revealed multiple communicating abscesses in the right side of the neck, posterior to the right submandibular gland extending to the para-pharyngeal, retropharyngeal, and anterior mediastinal compartments with multiple enlarged bilateral cervical and submandibular lymph nodes (Fig. 1, 2). The largest of these collections was seen in the right side of the neck posterior to the right submandibular gland measuring about 44 × 28 × 19 mm in craniocaudal, anteroposterior, and transverse diameters respectively. In view of the CT scan findings, surgical drainage was planned by a multidisciplinary team of otolaryngologists, cardiothoracic surgeons, anesthesiologists, and pediatricians.

On day 18 of admission, his preoperative workup revealed an isolated elevation of APTT (86.2 s), which was partially corrected after mixing studies to 64.4 s. Pediatric hematology consultation was sought, and the partially corrected APTT values were attributed to circulating anticoagulant antibodies. The patient did not develop any bleeding or thrombotic events during or after surgery.

On day 22 of admission, he underwent surgical drainage that revealed non-fluctuant swelling involving the right submandibular

region extending down to the right upper part of the neck and prevertebral region. Extensive necrotic tissue with matted and inflamed lymph nodes was identified and sent for histopathological evaluation, subsequently reported as only reactionary. No pus was drained.

On the fourth postoperative day, he was successfully extubated to room air. He received 1 dose of IV dexamethasone 0.15 mg/kg given stridor post-extubation, which improved after that. The patient continued to improve over time. Echocardiography was repeated before discharge that revealed mild ectasia of the left main coronary artery with mild dilatation. Finally, on day 31 of admission, he was discharged in stable condition with complete resolution of neck swelling and normal systemic examination.

Outcome and Follow-Up

Our patient underwent regular follow-up in general pediatric, pediatric cardiology, and ENT clinics post-discharge. He remained clinically well; his serial investigations revealed resolution of the inflammatory process, normalized coagulation profile, and resolution of coronary artery dilatation. Aspirin was continued for 6 months post-discharge and stopped after that.

Fig. 1. a Contrast-enhanced CT of the neck: axial view. **b** Contrast-enhanced CT of the neck: coronal view – arrow – retropharyngeal abscess.

Fig. 2. a Contrast-enhanced CT of the neck and chest: axial view at level of right upper cervical abscess. **b** Contrast-enhanced CT of the neck and chest: axial view level of right upper mediastinal abscess. **c** Contrast-enhanced CT of the neck and chest: coronal view corresponding to the right upper cervical and right upper mediastinal levels with axial view.

Given persistent noisy breathing and hoarseness of voice, outpatient nasopharyngoscopy was performed, and findings were consistent with mild subglottic granulations that resolved completely along with dysphonia on subsequent follow-ups. Subsequently, he was discharged from all subspecialty clinics after 18 months of discharge.

Discussion

We presented a case of a 9-month-old child with a challenging diagnosis and management of KD along with associated treatment complications. The otolaryngological presentation of KD remains quite frequent and may divert physicians in pursuing other relevant diagnoses causing significant delay in the initiation of treatment of KD [8–12]. According to a literature review by Cavicchiolo et al. [13], of 16 reported cases of atypical

KD with retropharyngeal abscess, most of the cases were of males, with a shorter duration of fever upon presentation (<4 days) and signs of deep neck infections. Furthermore, they failed to respond to broad-spectrum IV antibiotics and no tissue fluctuance or purulent fluid collection was found among all those who underwent surgical exploration of the retropharyngeal space [13]. These findings are in conjunction with our case. However, contrary to the diagnostic challenges encountered in these cases due to later manifestation of signs of KD, including coronary artery involvement seen on the ECHO, the clinical diagnosis of our patient was well established on day 5 of fever onset with the fulfillment of the American Heart Association's diagnostic criteria for complete KD [2] and immediate treatment with high-dose IVIg was commenced.

IVIg resistance in KD is an evolving albeit widely studied subject and is defined variably across literature as ei-

Table 2. Correlating IVIg resistance scores with our patient

Parameters	Kobayashi score ^a (cut-off: >5)		Egami score ^b (cut-off: >3)		Sano score ^c (cut-off: 2/3)		Kawanet score ^d (cut-off: 2)	
	criteria	points	criteria	points	criteria	points	criteria	points
Duration of illness, d	<4	2	<4	1	–	–	–	–
Time to treatment, d							<5	1
Hepatomegaly	–	–	–	–	–	–	+	1
Transaminases, U/L	ALT > 100	1	ALT > 80	2	AST > 200	1	ALT > 30	1
PLT	<300,000	1	<300,000	1	–	–	–	–
Inflammatory markers, mg/dL	CRP > 10	1	CRP > 8	1	CRP > 7	1	–	–
Age at onset, m	<12	2	<6	1	–	–	–	–
Serum Na, mmol/L	<133	2	–	–	–	–	–	–
Neutrophils, %	>80	2	–	–	–	–	–	–
Lymphocytes, /mm	–	–	–	–	–	–	<2,500	1
TSB, mg/dL	–	–	–	–	TSB > 0.9	1	–	–
Our patient	–	5	–	1	–	2	–	3

PLT, platelets; Na, sodium; TSB, total serum bilirubin; CRP, C-reactive protein. ^aKobayashi et al. [15]. ^bEgami et al. [17]. ^cSano et al. [18]. ^dPiram et al. [25].

ther recrudescence or persistence of fever at 24–48 h following the first IVIg infusion [14]. Various predictive scores aimed mainly for the Japanese population with good sensitivity (77–86%) and specificity (67–86%) exists to identify the individuals at-risk of IVIg resistance [15–18]. These include Kobayashi Score, Egami, and Sano scores [15–18]. However, due to the limitation of ethnicity, these scores do not yield similarly sensitive results for North American, European, and other Asian populations [19–24]. There are particularly no data from the Middle Eastern region involving the Arab population. Piram et al. [25] developed a scoring system named Kawanet based on a broad ethnic mix of patients with KD at a multi-center study in France that reported sensitivity of 80% and specificity of 65% for the North African/Middle Eastern population. A low total sample size of refractory KD cases (and an unknown number of Middle Eastern patients from the total cases remain barriers to its broader region-specific applicability. Despite its increasing reported incidence (10–20% of KD patients), and a significantly higher likelihood for coronary artery aneurysms, it is not a routine clinical practice to implement IVIg resistance scoring systems in non-Asian countries as a screening tool to identify the patients at a higher risk of developing refractory KD. The management guidelines for high-risk patients identified via scoring systems mainly advocate for concomitant use of corticosteroids with the second dose of IVIg to achieve earlier fever control but does not necessarily improve the coronary outcomes [14, 15, 26]. It is also noteworthy that the evidence for these treatment

consensuses is mainly generated via Japanese population-based scoring systems [15–18] and their implications on the other ethnic groups remain debatable [14].

Our patient exhibited resistance to the first dose of IVIg with non-resolution of fever 48 h post-infusion and hence required a second dose of IVIg succeeded by a 3-day pulse dose regime of systemic corticosteroids, following which his fever subsided, and he did not develop any progression of coronary artery lesions. He was retrospectively identified at high-risk of IVIg resistance based on the Kobayashi score and the Kawanet score (Table 2).

The autoimmune-mediated hypercoagulable and prothrombotic mechanisms that predispose an individual of KD to cardiac complications are less well understood. A possible explanation is that the endothelial damage caused by the circulating antibodies compounded by the proinflammatory cytokines fosters the hypercoagulable state [27, 28]. As the IVIg treatment ameliorates the inflammatory process, it is postulated to improve the hypercoagulable state manifested by the coagulation profile improvement [28, 29].

Our patient showed a similar initial improvement in his coagulation profile after receiving treatment with IVIg and corticosteroids, but then had an isolated increase in the APTT to 86.2 s. On day 16 of admission that gradually increased to a maximum value of 115 s on day 20 and thereafter showed a declining trend over 3 months to return to its baseline value. Cross-mixing studies showed partial correction suggesting inhibitory antibodies, which was confirmed by the detection of lupus anti-

coagulant. Although lupus anticoagulant is strongly associated with the risk of thrombosis in patients with antiphospholipid syndrome, its presence in patients with KD has only been described in one Japanese case report [30]. Despite the highly prolonged APTT and presence of thrombotic anticoagulants, the patient did not develop any bleeding or thromboembolic complications.

Conclusion

Given the atypical presentation of KD, physicians should always keep a high-index of clinical suspicion combined with serial physical examinations to aid in detecting the disease early. Furthermore, due to the absence of an ethnicity-specific scoring tool for identifying high-risk patients for refractory KD, all available scientific evidence correlating with clinical, biochemical, and radiological parameters should be utilized to arrive at the best possible treatment options. As the understanding of the pathophysiology evolves, clinicians should also be wary of the atypical complications that may arise either from the disease or its treatment. Future studies are required to understand the demographics, pathophysiology, and clinical manifestation of KD in Arab population to devise more sensitive and specific screening tools for detecting patients at high-risk of IVIg resistance.

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Statement of Ethics

This case report has been written in compliance with the ethical standards of the World Medical Association Declaration of Helsinki. Ethical approval was not required for the publication of this case report according to the guidelines of the Dubai Scientific Research and Ethics Committee. Written informed consent was obtained from parents for publication of the details of their child's medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.A.: case summary, literature review, and initial draft of the manuscript. F.A.M.: literature review, final draft, and editing of the manuscript. A.M.: critical reviewing of the manuscript. M.A.A.: critical reviewing of the manuscript and supervising the publication.

Data Availability Statement

All data generated or analyzed during this case report are included in this article. Further inquiries can be directed to the corresponding author.

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