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CASE BASED REVIEW

Kawasaki disease and immunodeficiencies in children: case reports and literature review

Francisco Rivas-Larrauri[1] · Lorena Aguilar-Zanela[1] · Paola Castro-Oteo[1] · Luis Adrian Rosales-Hernandez[1] · Francisco Otero-Mendoza[2] · Gabriela López-Herrera[3] · Javier Ordoñez-Ortega[2] · Martín Garrido-García[4] · Marco Antonio Yamazaki-Nakashimada[1]

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Abstract
Kawasaki disease (KD) has features that appear supporting an infectious cause with a secondary deranged inflammatory/autoimmune response. The association of KD in adults with human immunodeficiency virus infection and the presence of KD in patients with immunodeficiency disorders support the infectious theory. We present four KD patients associated with immunodeficiencies: one with X-linked agammaglobulinemia, one with HIV infection, and two with leukemia; one of these patients also had Down syndrome. We did a literature search to find out all reported cases of immunodeficiency with KD in children. In immunodeficiency disorders, the inability of the immune system to eradicate the pathogens coupled to an exaggerated inflammatory response, especially in chronic granulomatous disease, may lead to the development of KD. The study of patients with immunodeficiencies complicated with KD may shed light into the etiopathogenesis of the disease.

Keywords Kawasaki disease · Intravenous immunoglobulins · Immunodeficiency · Primary immunodeficiency disorders · HIV · Malignancy

Background

Kawasaki disease (KD) has features that appear supporting an infectious cause with a secondary deranged inflammatory/autoimmune response [1, 2]. Many features of the disease evoke childhood exanthems of infancy and epidemiological data show that KD has been associated with epidemics and clusters of the illness throughout the world [1, 2]. The abrupt onset of fever, conjunctival injection, pharyngeal erythema, cervical adenopathy, and the rash are clinical findings that are present in KD and various infections. The association of KD in adults with HIV and the presence of KD in patients with immunodeficiency disorders support the infectious theory [3]. We present four KD patients associated with immunodeficiencies: one with X-linked agammaglobulinemia (XLA), one with Human Immunodeficiency

✉ Marco Antonio Yamazaki-Nakashimada
yzki71@yahoo.com.mx

Francisco Rivas-Larrauri
rivaslarrauri@yahoo.com

Lorena Aguilar-Zanela
dra.jackyzanela@gmail.com

Paola Castro-Oteo
paolacastrooteo@gmail.com

Luis Adrian Rosales-Hernandez
telurio17@gmail.com

Francisco Otero-Mendoza
droterom@yahoo.com

Gabriela López-Herrera
lohegabyqbp@gmail.com

Javier Ordoñez-Ortega
malookim83@gmail.com

Martín Garrido-García
luismartin_garr@hotmail.com

1 Clinical Immunology Department, Instituto Nacional de Pediatría, Insurgentes Sur 3700-C, Col. Insurgentes Cuicuilco, 04530 Mexico City, Mexico

2 Pediatric Infectology Department, Instituto Nacional de Pediatría, Mexico City, Mexico

3 Immunodeficiencies Research Unit, Instituto Nacional de Pediatría, Mexico City, Mexico

4 Pediatric Cardiology Department, Instituto Nacional de Pediatría, Mexico City, Mexico

Virus (HIV) infection, and two with leukemia, and one of these patients also had Down syndrome (DS). We review the association of KD and immunodeficiencies. The study of patients with immunodeficiencies complicated with KD may shed light into the etiopathogenesis of the disease.

Case 1

A 10-year-old male was admitted to hospital with fever and rash, and he had a diagnosis of HIV infection at 3 months of age. After 4 days of fever, he developed dry lips, strawberry tongue, bilateral conjunctival injection, erythema on palms, and perineal erythema with desquamation. He had normal echocardiographic findings. Based on continuous fever, clinical, and laboratory abnormalities, he was diagnosed with KD. Intravenous immunoglobulins (IVIG) (2 g/kg) was administered with clinical improvement. Feet desquamation was present 3 days after IVIG infusion.

Case 2

A 3-year-old male patient presented with a history of weight loss. Physical examination revealed hepatosplenomegaly, and an ecchymosis in left iliac crest, a bone-marrow biopsy was diagnostic for acute myeloid leukemia (AML) and the first cycle of chemotherapy was started. He was hospitalized for pneumonia; during hospital stay, he developed fever, bilateral conjunctivitis, rash in the thorax and perineal area, cheilitis, cervical lymphadenopathy, and edema of hands and feet with palmoplantar erythema. Initial echocardiogram showed normal coronary arteries. The diagnosis of KD was established and treatment with IVIG at 2 g/kg/day and methylprednisolone at 0.7 mg/kg/day was initiated. He had fungemia with positive blood cultures for yeast. Repeated echocardiogram showed pericardial effusion and a left coronary artery (LCA) with ectasia in its emergence and aneurysm at the bifurcation site (LCA 4.1 mm, *Z*-score 5.57) with ectasia of the anterior descending coronary artery. He continued to have fever and hepatosplenomegaly. Laboratory tests revealed ferritin 12,094 mg/dL, 43,000 platelets with neutropenia and anemia and triglycerides of 298 mg/dL. A diagnosis of macrophage activation syndrome was done, and despite IVIG, cyclosporine and chemotherapy with Ara-C, daunorubicin and etoposide the patient died.

Case 3

A 2-year-old male with Down syndrome developed fever and rash. On physical examination, he had cheilitis, "strawberry tongue", hyperemic pharynx, multiple lymphadenopathies in the neck, erythema at the BCG scar, and erythema in the perineal region. Echocardiogram demonstrated pericardial effusion and normal coronary arteries. Diagnosis of incomplete KD was established. He was treated with IVIG (2 g/kg) and aspirin; his fever resolved 48 h later with decrease in CRP levels; however, he developed refractory thrombocytopenia (platelet count between 17,000 and 27,000). A bone-marrow aspiration showed findings compatible with acute myeloid leukemia.

Case 4

An 8-month-old presented with fever, rash, cough, and hoarseness. He had a family history of one maternal uncle that died in infancy because of sepsis, and another maternal uncle diagnosed as XLA who died secondary to cancer as an adult. Laboratory tests revealed Hb 11.4, WBC 4400/mm^3, lymphocytes 62%, neutrophils 4%, 1,104,000/mm^3 platelets, albumin 2.1, and BNP 469 pg/ml (< 100 nl), with IgG < 320 mg/dL, IgM 34 mg/dL, IgA < 5 Mg/dL, and CD19 1% (< 20). Echocardiogram revealed pericardial effusion, LCA ectasia 3.4 mm ($z > 4$). Blood cultures were positive for *Pseudomonas aeruginosa* and PCR for rhinovirus was positive. BTK expression was absent in the Western blot analysis confirming the diagnosis of XLA. The patient received IVIG, corticosteroids, and antibiotics with good response.

Search strategy

We conducted a literature search using Pubmed, MEDLINE, EMBASE, Web of Science, and Scopus databases including combination of terms "immunodeficiencies", "primary immunodeficiency disorders", "hypogammaglobulinemia", "Leukemia", "Malignancy", "Kawasaki disease", "Down syndrome", and "HIV". The search period was extended until April 2019 of articles written in English. We reviewed the abstracts and retrieved appropriated cases. We also scrutinized the reference list of the included studies to identify additional references (Fig. 1). We scanned the titles and abstracts for the following inclusion criteria: (1) cases of KD associated with immunodeficiencies in children (primary immunodeficiency disorders, malignancy, or HIV) and (2) published in a peer-reviewed journal. Cases where malignancy appeared after KD or did not present immunodeficiency were excluded. The following data were extracted from the studies: authors, publication year, type of KD, clinical features, laboratory studies, cardiac complications, and outcomes.

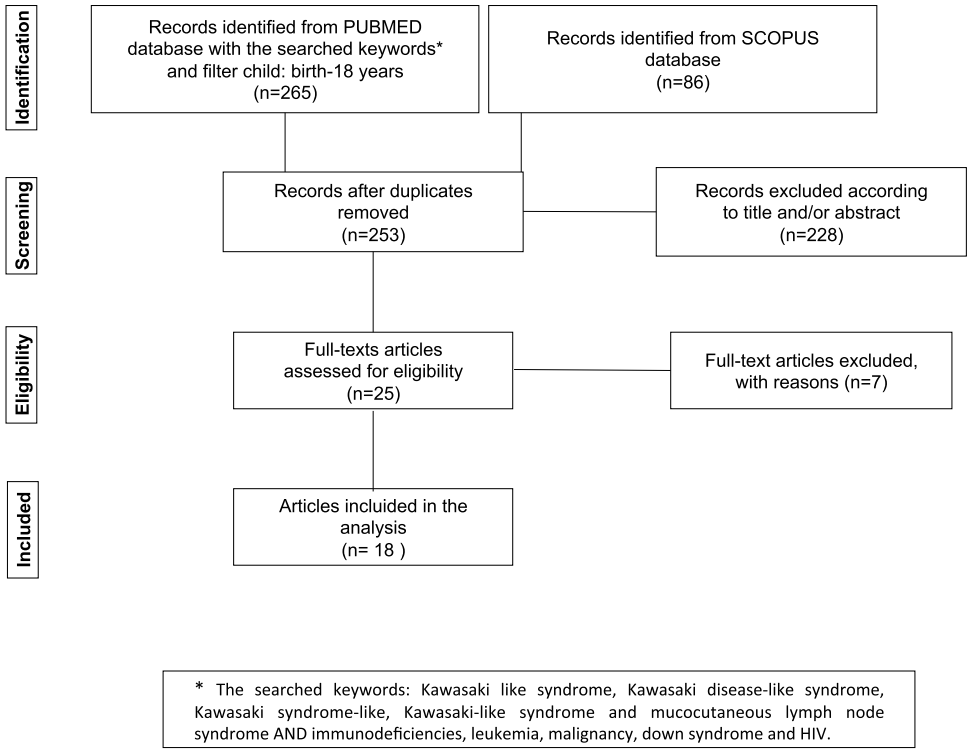

Fig. 1 Flow chart of study selection

Discussion

KD has been described as a complication of diverse primary and secondary immunodeficiency disorders. Nineteen studies were found reporting 40 patients (Table 1) [3–20]. A vast majority of the patients were male 87.5% (21/24) due to the fact that three primary immunodeficiency disorders associated with KD are X-linked [chronic granulomatous disease (CGD), XLA, and Wiskott–Aldrich syndrome (WAS)]. Incomplete KD was present in 54% (20/37) of the patients compared to 10% described in the literature [21]. More than half of the patients presented with cardiac alterations, with nine presenting coronary abnormalities (52% 10/19). BCG erythema, perineal erythema, and thrombocytosis were valuable clues to make the diagnosis. Only five patients were infants.

KD can present as a complication of patients with lymphocyte, phagocyte, and antibody defects [3–17]. Fourteen patients presented a primary immunodeficiency disorder, and 25 patients a secondary immunodeficiency (4 leukemia, 4 HIV infection, and 17 DS).

Upon reviewing the literature, CGD patients were overrepresented [3–6]. This may be related to the hyperinflammatory response that is observed in this disease [22]. CGD and KD share some common features such as neutrophil activation and an increased number of neutrophils in the peripheral blood. Both can be complicated with macrophage activation syndrome [23, 24]. A master role of neutrophils has been implicated in the etiopathogenesis of KD [25]. In KD, there is an initial neutrophilic predominance in peripheral blood and arterial tissues compatible with an innate immune response to an infection, followed by a T-lymphocytic and IgA plasma cell infiltrates in acutely inflamed KD coronary arteries demonstrating a robust acquired immune response [1]. NADPH-oxidase deficiency has been shown to enhance the release of IL-1α in response to damaged cells, promoting an excessive G-CSF-regulated neutrophils response and prolonged inflammation [26]. Th17 cells are also high in both KD and CGD [22].

Reports of KD in XLA patients argue against the presence of autoantibodies in the pathogenesis of KD; however, different mechanisms of disease may be present with different subtypes of KD patients. Inflammatory diseases are increased in XLA patients compared to the general population [27]. BTK is expressed in lymphoid and myeloid cells and has been implicated in the regulation of inflammation [28]. PBMCs from XLA patients produce increased levels of TNF-α, IL-6, IL-10, and IL-1α in response to LPS stimulation [29]. Contrasting with this, BTK has recently been identified as a direct regulator of the NLRP3 inflammasome, in which the NLRP3 inflammasome activity has been found to be impaired in BTK-deficient patients [30]. Our patient is the fourth patient with XLA complicated with KD. In our case, the AHA guidelines to diagnose incomplete presentations were very helpful, since only transient rash and prolonged fever were present [31]. We documented Pseudomonas infection in our patient and these bacteria have been described as a presenting manifestation of XLA, and in

Table 1 Kawasaki disease in children with immunodeficiencies

Author	Diagnosis	Diagnosis of KD	Age	Gender	Infection	Cardiac involvement	Laboratory tests	Treatment	Outcome
Yamazaki-Nakashimada et al. [3]	CGD	Incomplete	1 years	M	Pneumonia	Left and right coronary arteries ectasia	Hb 12.4 g/dL, WBC 14,100/mm^3 (75% lymphocytes, 25% neutrophils), 285,000/mm^3 platelets	IVIG, ASA, metylprednisolone	Remission
Hule et al. [6]	CGD (p47 phox)	Incomplete	10 years	F	Hypoechoic foci liver	Left ventricle systolic dysfunction	WBC 15,400 cells/mm^3 ESR 57 mm/h, CRP of 240.9 mg/L (normal 0–6 mg/L)	IVIG 2 g/kg/day, ASA, enalapril, and inotrope support was given.	Remission
		Incomplete	2 years	M	No	Moderate left main coronary artery di-lation	Hb 7.7 g/dL, ESR of 95 mm/h and CRP 98.55 mg/L	IVIG 2 g/kg/day and ASA.	Remission
Tsuge et al. [5]	CGD (gp91 phox)	Complete	10 months	M	No	Normal	Hb 9.7 g/dL, WBC 16 000 cells/mm^3, with 52.0% neutrophils, 38.6% lymphocytes, and 8.3% monocytes), 466,000/mm^3. CRP 17.1 mg/dL	IVIG infusion (2 g/kg for 24 h) and flurbiprofen treatment (5 mg/kg daily) were initiated. He was treated with additional IVIG infusion (1 g/kg/day for 12 h) 5 mg/kg of ASA daily.	Reactivation
Muneuchi et al. [4]	CGD	Incomplete	2 years	M	No	Dilatation of the left main coronary artery at a maximum diameter of 4 mm	Hb 11. 6 g/dL, WBC 10 300/mm^3 (61% of neutrophils and 29% of lymphocytes), platelets 188,000/mm^3, CRP 3.84 mg/dL	IVIG 2gkgdo. ASA and dipyridamole. He was retreated with additional IVIG (1 g/kg/day for 2 days)	Reactivation
Anzai et al. [12]	IgA A deficiency	Complete	5 years	M	No	Normal	WBC 12,600/mm^3; CRP 3.59 mg/dL; ESR 76 mm/h	ASA 50 mg/kg/day and intravenous urinastatin 50,000 U×6/day. CsA (3.0 mg/kg/day)	Remission

Table 1 (continued)

Author	Diagnosis	Diagnosis of KD	Age	Gender	Infection	Cardiac involvement	Laboratory tests	Treatment	Outcome
Nishikawa et al. [11]	Selective IgA deficiency	Complete	2 years	M	No	Normal	WBC 11 800 cell/mm^3, CRP 8.6 mg/dL; ESR 100 mm/h), hyponatremia and hyperbilirubinemia	ASA (30 mg/kg per day) and urinastatin (15 000 U/kg per day) (methylprednisolone 30 mg/kg per day for 3 days)	Remission
Sharma et al. [8]	XLA	Incomplete	3 years	M	No	Normal	Hb 8.8 g/L; WBC 10.33×109/L; N 50%, L 40%, M 8%,Eo 2%; plateles 1280×109/L; ESR 48 mm; CRP 46 mg/L	IVIG 2 g/kg and ASA 50 mg/kg/day	Remission
Malekzadeh et al. [10]	XLA	Incomplete	3 years	M	Gram negative bacilli	Myocarditis	ND	IVIG and metylprednisolone plus therapy	Reactivation
Behniafard et al. [9]	XLA	Incomplete	15 months	M	No	Normal	Albumin 2.8 g/dL, WBC 20,260/mm^3	IVIG	Remission
Şanlidag et al. [14]	Transient hypogammaglobulinemia of infancy	Incomplete	4 years	M	No	Normal	WBC 24,000/mm^3, 808,000/mm^3 platelets	IVIG and ASA 30 mg/kg/day.	Remission
Kimata [7]	HIES	ND	3 years 2 years	M F	ND ND	ND	ND	IVGG at 400 mg/day for 5 days	Remission
Kawakami et al. [13]	WAS	Complete	6 months	M	ND	ND	ND	IVIG 1 g/kg× 2 days	Remission
Lee et al. [19]	Acute myelogenous leukemia	Incomplete	11 months	M	No	Dilation of the right coronary artery (RCA 2.2 mm, *z*-score 2.15) and left main coronary artery without aneurysm	Low sodium 129 mmol/L, low chloride 95 mmol/L, low albumin 3.3 g/L, LDH 3253 μ/L, ferritin of 1992 ng/mL slightly elevated liver function tests, and significantly elevated CRP and ESR	IVIG	Remission

Table 1 (continued)

Author	Diagnosis	Diagnosis of KD	Age	Gender	Infection	Cardiac involvement	Laboratory tests	Treatment	Outcome
Akita et al. [18]	Monocytic leukemia	Complete	11 years	M	No	Cardiomegaly and dilation of the left coronary artery (4 mm) with pericardial effusion	Platelets 417,000/mm^3	IVGI 200 mgkgday for 3 days and methylprednisolone 1.25 mg/kg/day for 3 days.	Remission
Nigro et al. [15]	Perinatal HIV 1 Infection. Postmortem	Complete	9 months	F	Parvovirus B19	Normal	Hb10.1 d/dL, WBC 6200× 10^6/l (N 44%, Eo 1%, M 1%, L 54%) 356,000/mm^3 platelets, ESR 30 mm/h and AST 352 IU/l.	Not treated	Dead
Aladhami et al. [16]	HIV Infection perinatal	Complete	3 years	M	ND	Normal	Platelets 318,000/mm^3	IVIG 2 g/kg and aspirin 100 mg/kg per day. And 10 days after admission, on ASA 5 mg/kg daily	Remission
Belostotsky et al. [17]	Perinatal HIV infection	Complete	14 years	M	No	No	ND	IVIG 2gkg	Remission
Takatsuki et al. [20]	Down syndrome	Incomplete in half the patients	16 children	ND	ND	ND	ND	IVIG 2 grkgdo. In patients with high risk score received IVIG, intravenous prednisolone (2 mg/kg) and ASA (30 mg/kg/day)	Remission
Case 1	HIV	Incomplete	10 years	M	Negative	Normal	Hb 14.1 g/dL, WBC 12,300/mm^3, 9100 neutrophils, 1400 lymphocytes, 1700 monocytes, platelets 259,000/mm^3, CRP 5.9 mg/dL (normal 0.07-0.8), AST 19 U/L, A LT 35 U/L albumin 3.1 g/dL	IVIG 2 g/kg/d, ASA 30 mgkgd	Remission

Table 1 (continued)

Author	Diagnosis	Diagnosis of KD	Age	Gender	Infection	Cardiac involvement	Laboratory tests	Treatment	Outcome
Case 2	Acute myeloid leukemia	Complete	3 years	M	Candida	Pericardial effusion and a left coronary artery with ectasia in its emergence and aneurysm at the bifurcation site mm, Z-score 5.57 with ectasia of the entire anterior descending artery	Hemoglobin 6.4 g/dL, WBC 9200× 10^3/μL, neutrophils 1110× 10^3/μL, lymphocytes 2800× 10^3/μL, 18,000 platelets/μL, 49% blasts in peripheral blood; dehydrogenase (LDH) 2292 mg/dL.	IVIG, corticosteroids, cyclosporine, etoposide	Refractory, death
Case 3	Down syndrome, leukemia	Incomplete	2 years	M	Negative	Pericardial effusion and normal coronary arteries	Hb 10.6 g/dL, WBC 9.1×10^3/μL, 49,000/mm^3 platelets, ESR 54 mm/h, CRP 3.7 mg/dL, LDH 263 mg/dL, albumin 2.9 g/dL, TP 12.1 s, INR 1.03, TPT 41.2 s, fibrinogen 525 mg/dL, pro-BNP 1730 pg/ml	IVIG, ASA	Remission of KD
Case 4	XLA	Incomplete	8 months	M	*Pseudomonas aeruginosa,* rhinovirus	Pericardial effusion, LCA ectasia 3.4 mm (z > 4).	Hb 11.4, WBC 4400/mm^3, lymphocytes 62%, neutrophils 4%, 1,104,000/mm^3 platelets, albumin 2.1, BNP 469 pg/ml (< 100 nl), with IgG < 320, IgM 34, IgA < 5, CD19 1% (< 20)	IVIG, corticosteroids, ASA	Remission

ASA aspirin, *ESR* erythrocyte sedimentation rate, *IVIG* iv human gamma globulin, *ND* no data, *WBC* white blood cell, *PC* Platelet count, *XLA* X-linked agammaglobulinemia, *WAS* Wiskott–Aldrich syndrome, *CGD* Chronic granulomatous disease, *HIES* Hyper-IgE recurrent infection syndrome, *MAS* macrofaghe activation syndrome, *CsA* cyclosporine, aspirin

the past, it has been associated with KD [32, 33]. Two CGD patients and two XLA patients needed additional treatment to control KD, reflecting the hyperinflammatory proclivity of both diseases (Table 1).

Although up to 70% of WAS patients present autoimmunity or autoinflammatory complications including systemic vasculitis with aneurysm formation and Henoch Schonlein purpura, only one patient with WAS has been reported with KD [13, 34]. Two patients with Hyper-IgE syndrome (HIES) and KD have been reported [7]. Interestingly, a number of HIES patients present coronary artery aneurysms; however, the previous KD in these patients have not been documented, and these vascular abnormalities are considered a feature of HIES [35]. Th17 cells are low in HIES contrasting with elevated Th17 cells seen in KD. Autosomal recessive transducer and activator of transcription-2 (STAT-2) deficiency is a recently described inborn error of immunity with susceptibility to virus [36]. Some of these patients present with inflammation after the administration of vaccine-strain measles [36]. Hambleton et al. reported a 5-year-old boy with disseminated vaccine-strain measles, who 6 days after vaccination at 18 months, he developed a Kawasaki-like disease with fever, rash, conjunctivitis, and lymphadenopathy complicated with pneumonitis and hepatitis. Vaccine-strain measles was detected in the lung and blood [36].

The most convincing evidence that immunodeficiency predispose to the development of KD comes from the study of adults with the disease. KD is rare in adults and it has been reported that about one-third of adult KD are associated with HIV infection [37–49]. More than 20 cases of HIV patients with KD have been reported. An infection with ineffective clearance of the microbe by the defective immune response may lead to persistent inflammation and the development of KD. In HIV, superantigens produced by HIV may interact with T cells and induce vasculitis. Etiopathogenic similarities between HIV infection and KD exist: an increase in serum soluble CD8, activation of B cells, and an increase in proinflammatory cytokine levels. It has also been postulated that KD in HIV is the result of the reactivation of a viral infection. Intriguingly, KD has rarely been described as a complication of HIV in children, with our patient 1 being the fourth case with this association [15–17]. The youngest case described to date is a 3-year-old male who presented HIV and KD with an uneventful evolution.

In our second case, with the presence of fever, rash, lymphadenopathy, serositis, hepatosplenomegaly, hyperferritinemia, and pancytopenia, systemic–onset juvenile idiopathic arthritis (SoJIA) complicated with MAS should be considered in the differential diagnosis. In fact, SoJIA cannot be easily distinguished from incomplete KD in infants, since many features overlap (including coronary abnormalities) and neither KD nor SoJIA has diagnostic laboratory tests [50, 51].

The association of KD with malignancy has seldom been described [52, 53]. An 11-year-old boy who was diagnosed with acute monocytic leukemia who presented KD complicated with pericardial effusion and left coronary dilation 1 week after chemotherapy [18]. An infant with ALL presented BCG reactivation and possible incomplete KD [54]. DS has been associated with leukemia; however, the coexistence of DS with KD is very rare, with only four children with DS in 18,492 KD patients according to a Japanese nationwide survey [20]. The association of immunosuppression caused by leukemia, immunosuppressant medications, DS, and HIV could have been linked to the development of KD in our patients.

The exact classification of KD has long been debated, as the disease has been classified as an infectious, autoimmune, or autoinflammatory disorder. There is evidence supporting all three, and they are not mutually exclusive, as the disease can be considered an infectious driven disease with an aberrant autoimmune/autoinflammatory response against self, predominantly to the arteries [2].

In conclusion, in immunodeficiency, the inability of the immune system to eradicate the pathogens and an exaggerated inflammatory response, particularly in CGD and XLA, may lead to the development of KD. Patients with immunodeficiencies frequently present an incomplete form of KD. The association of immunodeficiencies with KD supports the infectious etiology of the disease. Patients with primary and secondary immunodeficiencies may develop KD and the diagnosis should be considered to avoid complications.

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Author contributions Case 1 was diagnosed and followed up by LAZ, PCO, LARH, JOO and MAYN. FRL, MGG, and MAYN were involved in the caring of Case 2 and Case 3, and Case 4 was diagnosed and followed up by FOM, GLH, and MAYN. LAZ, PCO, LARH, and MAYN wrote the manuscript. Literature data were searched and analyzed by all the authors. The final version was read corrected and approved by all the authors.

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Compliance with ethical standards

Conflict of interest Dr. Marco Antonio Yamazaki-Nakashimada has received lecture fees from Shire, CSL Behring and Octapharma, and the other authors declare that they do not have any conflict of interests.

Ethical approval All the procedures performed in this study were in accordance with the ethical standards of the institutional and or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Written informed consent was obtained from the patients for publication of the case reports.

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