

TB or not TB: a confusing case



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Patient Presentation

A previously well 17 month old boy presents with a three day history of fever and a skin rash. No accompanying cough or diarrhoea.

Acknowledgements:

Dr Christiaan Scott and Dr Kate Weakley Webb, Paediatric Rheumatology, Red Cross War Memorial Children's Hospital, University of Cape Town, South Africa.

Partnership

We have partnered with The International Union of Basic and Clinical Pharmacology (IUPHAR) to bring you in-depth information about drugs and pharmacology with links to the Guide to ImmunoPharmacology.

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History

The patient and his family recently moved to South Africa from Burundi (Eastern Africa). His mother reports that prior to this presentation the child has been well. She is unaware of him having any contact with TB or other infectious illnesses.

According to his Road to Health Card he was born full term from a normal vaginal delivery with no complications noted.

He was breast fed for the first 10 months.

He is noted to be HIV unexposed, but no [PCR](#) had been done to

confirm this.

All growth parameters have been consistent and above the 50th centile for height and weight.

Past Medical History

- Nothing reported

Past Surgical History

- Nothing reported

Vaccination History

- BCG given at birth
- No other vaccination history available

Family History

- Lives with both parents and three older siblings aged 3, 5 and 8 in a 1 bedroom apartment with all amenities.

Allergies

- None known

Medication

- Nil

Travel History

- Recent road travel from Burundi to South Africa

Differential Diagnosis

Differential diagnosis of an otherwise well child with a rash and fever:

Infections:

Viral

- Measles
- Rubella
- Parvovirus
- Coxsackie
- HHV 7
- Varicella
- Adenovirus
- Rhinovirus
- Influenza
- Parainfluenza

Bacterial

- Scarlet fever
- Meningococcus
- Rickettsia
- Lyme disease

Autoimmune

- Post streptococcal
- Kawasaki disease
- Henloch-Schonlein Purpura

Malignancy

- Leukemia
- Lymphoma

Examination

In Admission:

Appearance

- Ill looking child, alert and awake
- Well nourished

Vitals

- Temperature: 40°C
- Heart rate: 105
- Respiratory rate: 25

General

- Normal weight
- No dehydration
- Warm peripheries
- Cervical and axillary lymphadenopathy

ENT

- Mild pharyngitis

Chest

- Chest clear

Cardiovascular

- Mild tachycardia

Abdomen

- Not distended
- Soft, no generalised tenderness
- No organomegally
- Bowel sounds present

Neurological

- Normal level of consciousness
- Alert and co-operative

Dermatological

- Generalised maculo popular rash

Child was admitted (see investigations), and discharged after 2 days on Amoxil, to be followed up at out patient clinic in 48

hours to have Mantoux test read

Nine days after initial presentation the patient again presents to hospital

Five days earlier, the patient was started on [TB treatment](#) following a positive Mantoux test and a suspicious looking chest X-ray. He now presents again with a fever and 7-day swelling of the face.

On Examination

- Ill looking child
- Temperature 39°C
- Generalized lymphadenopathy
- Lips swollen, drooling, red tongue and throat.
- Perioral peeling
- Periorbital dryness and erythema
- Warm swollen hands and feet, with painless palpable effusions over the ankles
- Swollen, red BCG vaccination site and red mantoux mark
- Peeling rash on trunk, neck and axillae

Patient was re-admitted, an echocardiogram was performed which was normal and he was treated with 2g polygam, paracetamol and 50mg aspirin daily (see investigations).

He improved and was discharged

10 days later the patient returned to hospital

Although he no longer had a fever his mother was concerned about the persistent rash all over his body and a recurrent swelling of his hands and feet, which had become painful, preventing the child from walking.

On Examination

- Ill looking child with marked irritability

- Apyrexial
- Swollen hands, feet and ankles, with +dactylitis.
- Generalized lymphadenopathy
- Generalized erythematous macular rash

Patient was readmitted

No repeat polygam given as patient had responded to the first dose

Patient was kept on 20mg daily [aspirin](#), [Ibuprofen](#) for pain and [sucralfate](#)

TB treatment was continued

(see investigations)

He was discharged home on Aspirin, pain medication and a temperature chart

One month later, patient was seen as an outpatient for a check up

The home temperature chart revealed no fever.

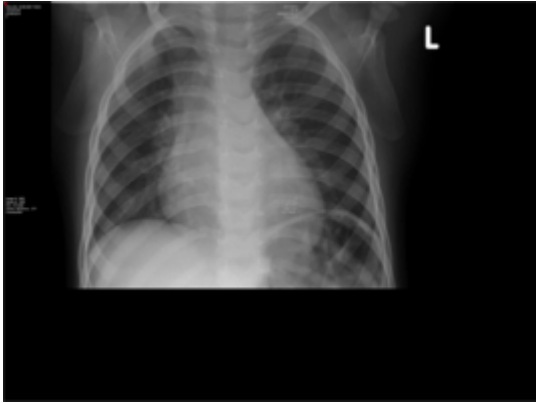
On Examination

- Apyrexial
- Lymphadenopathy had resolved
- Hands and feet were still swelling occasionally, but he was able to walk. Some residual desquamation was noted on the hands
- No joint involvement
- BCG and Mantoux sites were normal
- Pain medication was stopped
- TB medication was continued for the full course

Patient was booked for a 3-month repeat Echo

(see investigations)

Investigations



On Presentation

- Chest X-Ray- Widened mediastinum and hilar lymphadenopathy
- Mantoux performed based on CXR finding. Area of induration at 48 hours was >15mm and considered positive.



9 days later

- ESR 97
- HIV negative
- ASOT negative
- antiDNase negative

- TB gastric washings, repeated on three occasions- all negative
- Echocardiogram-normal

2 weeks later

- Repeat echocardiogram- normal
- ESR 75, CRP 15
- ANA negative
- Sickie test negative

Discussion

Introduction

This case focuses on an acutely ill 17-month-old baby boy who presented to a paediatric hospital in South Africa having recently moved from Burundi in eastern Africa. His initial presentation was of a rash, fever and pharyngitis, for which he was treated with oral antibiotics. A routine TB work up was done. Based on the hilar lymphadenopathy on chest X-ray, and a positive Mantoux test, he was started on TB treatment, despite not having a definitive microbiological diagnosis. As the paediatric hospital lies in an area with high TB prevalence, treatment is standard protocol. However within a few short days his signs and symptoms worsened.

Background

A diagnosis of Kawasaki Disease (KD) was made and the following discussion will focus on this acute multisystem vasculitis syndrome of unknown etiology. KD is seen predominantly in infants and children younger than 5 years of age and the disease occurs globally, having been first diagnosed in Japan in the 1960s.

KD is characterized by prolonged fever, conjunctivitis,

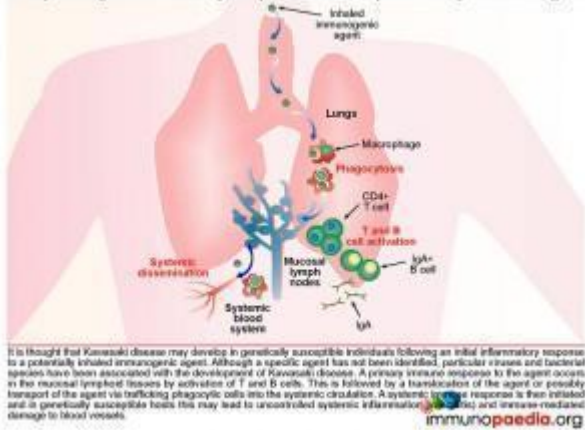
diffuse mucosal inflammation, polymorphous skin rashes, indurative oedema of the hands and feet with an associated peeling of finger tips and non-suppurative lymphadenopathy. The most severe complication in KD is that of acute coronary syndrome, including myocardial infarction and coronary artery aneurysms, which is pathognomonic when identified in the setting of a compatible febrile illness. To date, there are no specific diagnostic tests for KD, instead the diagnosis is made clinically by the presence of fever for five days and 4 out of 5 of the following criteria:

1. Non-purulent bilateral conjunctivitis
2. Cervical lymphadenopathy of nodes >1.5 cm
3. Polymorphous skin rashes
4. Strawberry tongue, fissured lips and/or diffuse erythema of the oropharynx
5. Oedema of the palms and soles and desquamation of the fingertips.

It has also been noted that in countries where newborn babies receive Bacillus Calmette-Guerin (BCG) vaccination, KD can be associated with erythematous induration or even ulceration of BCG scars in one-third of cases. The patient in this case study had received BCG at birth and during the course of his illness presented with BCG scar reactivation and a positive Mantoux test with a reading of >15mm.

Although the aetiology of KD is not well understood, with the aid of our case study and graphics we will explore the ways in which immune-mediated destruction of the vascular system occurs following the introduction of a yet to be identified immunogenic agent. We will also discuss the role that genetics has to play in this disease by looking specifically at two of the genes that have been implicated. We will also explain how this vasculitic syndrome may be connected to BCG scar reactivation and a positive Mantoux test in the absence of TB infection.

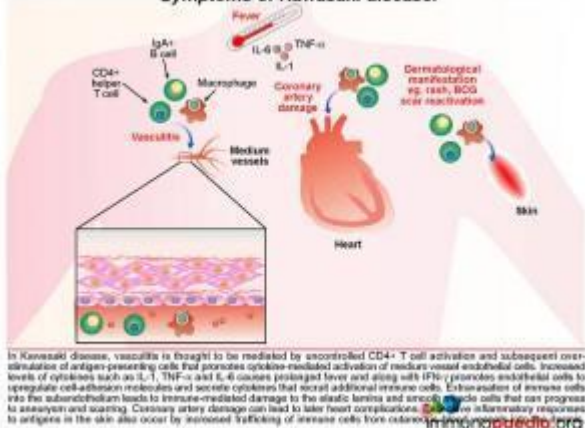
Precipitating inflammatory response due to potentially inhaled agent.



To better understand Kawasaki disease, let's first look at the precipitating inflammatory response

It is thought that KD may develop in genetically susceptible individuals following an initial inflammatory response to a potentially inhaled immunogenic agent. Although no specific agent has been identified, prior infection by one of a number of viruses and bacterial species has been associated with the development of KD. These include EBV, HIV, measles, *Staph. aureus*, *Strep. pyogenes* and *Mycoplasma pneumoniae*, to name a few. A primary immune response to the agent occurs in the mucosal lymphoid tissues by activation of T and B cells, which is then thought to be followed by a translocation of the agent or possibly transport of the agent via trafficking phagocytic cells into the systemic circulation. A systemic immune response is then initiated and in genetically susceptible hosts this may lead to the uncontrolled systemic inflammation and immune-mediated damage of blood vessels or vasculitis.

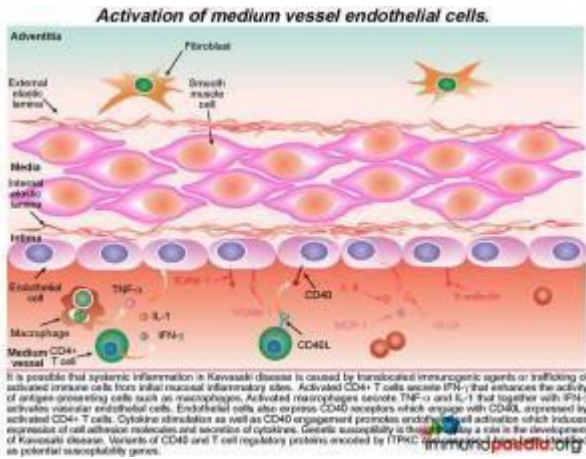
Symptoms of Kawasaki disease.



What are the signs of this developing vasculitis in Kawasaki Disease?

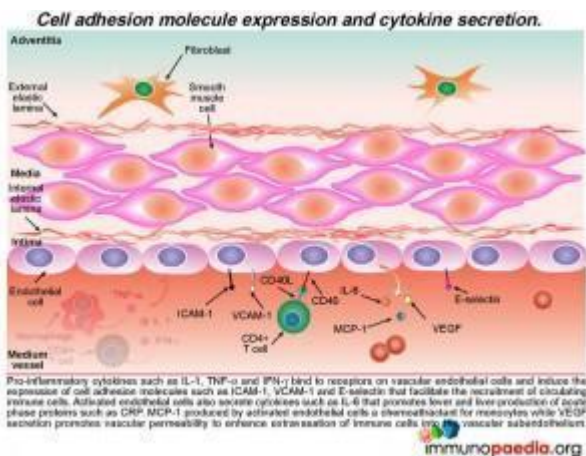
The ensuing vasculitis is thought to be mediated by uncontrolled activation of CD4+ T cells and antigen-presenting cells and subsequent cytokine-mediated activation of medium vessel endothelial cells. The increased levels of cytokines such as IL-1, TNF-alpha and IL-6 cause the prolonged fever as seen in this patient. Along with IFN-g, these pro-inflammatory cytokines promote endothelial cells to up-regulate cell-adhesion molecules and secrete cytokines that recruit additional immune cells. Extravasation of immune cells into the subendothelium leads to immune-mediated damage to the elastic lamina and smooth muscle cells. This weakens the blood vessel wall that in time can progress to aneurysm formation and scarring. When coronary arteries are involved it can result in ischaemic heart complications (not present in this patient). Excessive inflammatory responses to antigens in the skin also occur because there is increased trafficking of immune cells from cutaneous blood vessels into the dermis. This can result in a persistent generalized rash and BCG scar activation, as seen during the course of illness in our patient.

As we know KD is a multisystem vasculitic syndrome. In the acute stage, numerous immunologic factors including CD4+ T cell activation, cytokine production and enhanced adhesion molecule expression by endothelial cells mediate the vasculitis. These various processes are further discussed here.



Lets look more closely at the activation of medium vessel endothelial cells

The activated CD4+ T cells secrete IFN-g that enhances the activity of phagocytic cells such as macrophages. Activated macrophages secrete TNF-a and IL-1 that together with IFN-g activates vascular endothelial cells. Endothelial cells also express CD40 receptors, which engage with CD40L (CD154) present on the surface of activated CD4+ T cells.



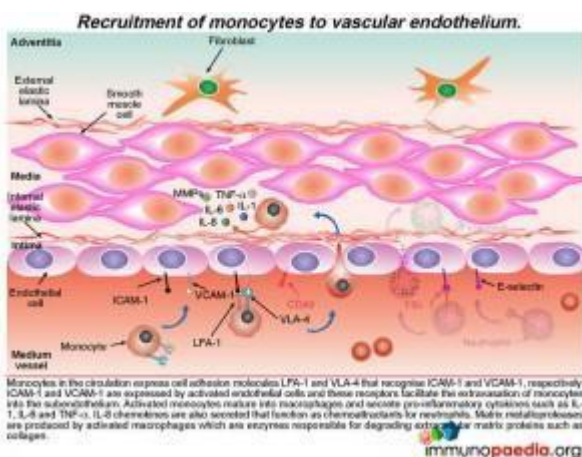
The resulting tethered CD4+ cells to the vascular endothelium secrete cytokines, which further activates the endothelial cells and induces them to express further cell adhesion molecules (ICAM-1, VCAM-1 and E-selectin) and secrete IL-1, TNF-a and IFN-g. Genetic susceptibility is thought to play a role in the development of Kawasaki disease. In particular, polymorphisms in two genes encoding the T cell regulatory protein ITPKC and Caspase-3. We will uncover these specific

events towards the end of our discussion.

Activated endothelial cells also secrete IL-6 in sufficient amounts to promote fever by acting on the hypothalamus and to induce the liver to synthesize acute phase proteins (such as CRP). MCP-1 is a chemo-attractant for monocytes and VEGF promotes vascular permeability and enhances extravasation of immune cells into the sub-endothelium.

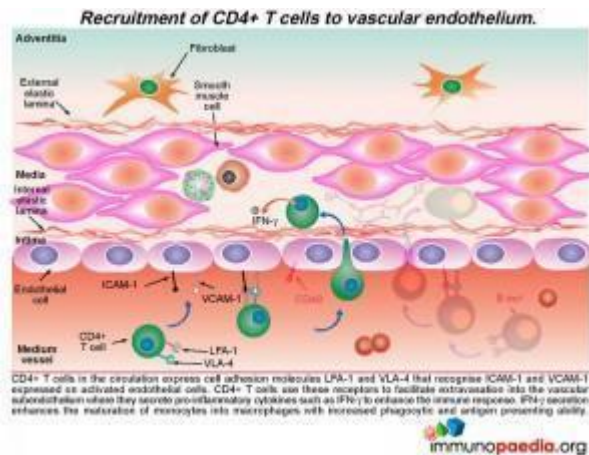
Recruitment of monocytes and neutrophils to the endothelium

Activated monocytes, recruited to the sub-endothelium by interacting with the adhesion molecules (ICAM-1 and VCAM-1) on endothelial cells, mature into macrophages and secrete pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α .



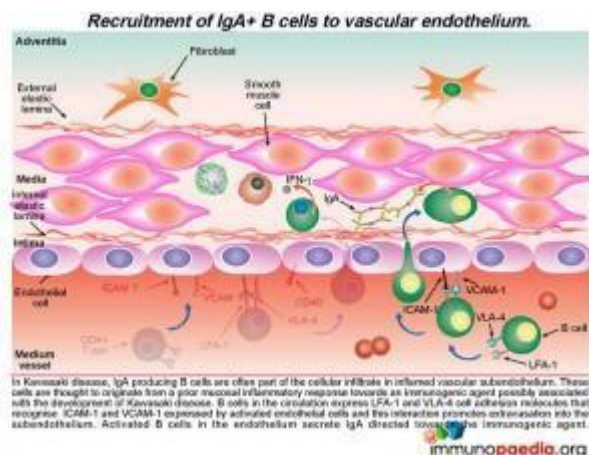
Neutrophils are also recruited to the activated endothelium by recognition of E-selectin that binds to ESL-1. Neutrophil recruitment is enhanced by IL-8, a chemokine released by activated monocyte / macrophages. Neutrophils then extravasate into the subendothelial tissue

where they secrete elastase, a serine protease that degrades elastin of connective tissue. Activated monocytes / macrophages release matrix metalloproteases, protease enzymes that degrade extracellular matrix proteins, such as collagen. How this damages the subendothelium is discussed in greater detail a little later.



The recruitment of CD4+ T cells to the endothelium occurs in a similar way

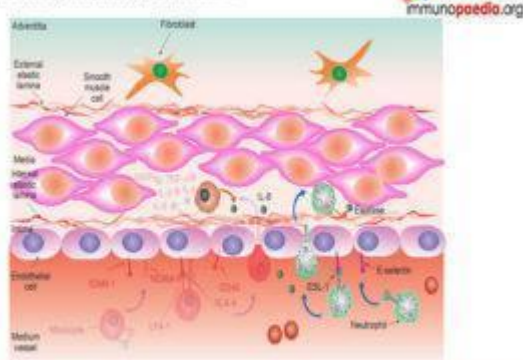
Additional CD4+ T cells in the circulation that express cell adhesion molecules LFA-1 and VLA-4 bind to ICAM-1 and VCAM-1 that are expressed on activated endothelial cells. This CD4+ T cell interaction facilitates extravasation into the subendothelium where they further secrete IFN-γ, which in turn, enhances the maturation of monocytes into macrophages with increased phagocytic and antigen presenting abilities.



Recruitment of IgA-secreting B cells to the endothelium

In KD, IgA producing B cells are also often part of the cellular infiltrate in the inflamed subendothelium. These are thought to originate from an earlier mucosal inflammatory response to the immunogenic agent, the probable trigger leading to KD. B cells in the circulation express LFA-1 and VLA-4 cell adhesion molecules that recognise ICAM-1 and VCAM-1

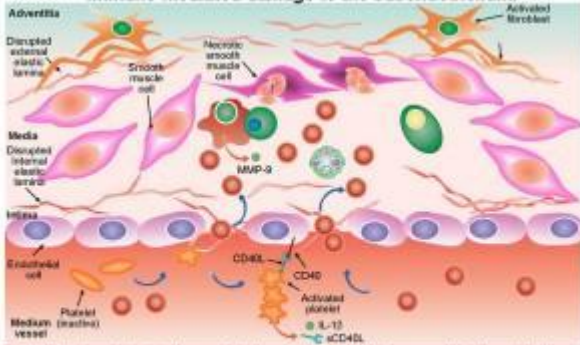
Recruitment of neutrophils to vascular endothelium.



Neutrophils in the circulation are recruited to activated endothelium by receptors of E-selectin that binds to ESX-1. IL-8 chemokines released by activated immune cells in the subendothelium also serve as chemotactants for neutrophils. Neutrophils extravasate into the subendothelial tissue where they secrete elastase, a protease enzyme that degrades extracellular matrix proteins.

expressed by activated endothelial cells and this interaction promotes B cell extravasation into the subendothelium. Activated B cells in the endothelium secrete IgA.

Immune-mediated damage to the subendothelium.



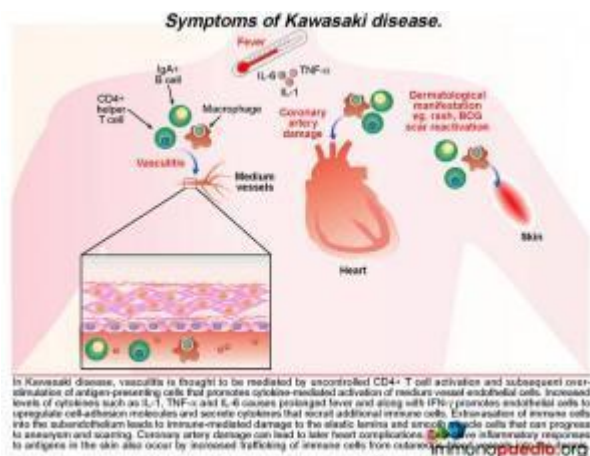
Increased infiltration and activation of immune cells in the subendothelium leads to immune-mediated damage to the tissue. The elastic lamina is degraded by the action of elastases and matrix metalloproteinases. These enzymes also digest extracellular matrix proteins that disrupt the smooth muscle architecture leading to necrosis of smooth muscle cells. Disrupted endothelial cell barriers allow the influx of erythrocytes into the subendothelium causing aneurysm development and thrombosis. Exposed collagen activates platelets which express CD40L. Engagement of CD40L with CD40 expressed by endothelial cells promotes platelets to secrete IL-1 and soluble CD40L. IL-1 and CD40L can promote further activation of endothelial cells thus increasing the severity of the vasculitis. Activated fibroblasts secrete extracellular matrix proteins such as collagen leading to vessel stiffness and coronary artery damage that may contribute to heart failure.

Immune-mediated damage leading to aneurysm and scarring

The result of this mass movement of activated cells and the effects of cytokines is damage and dissolution of the subendothelium tissues. The elastic lamina is degraded by the action of elastases and matrix metalloproteases and these enzymes also digest extracellular matrix proteins that disrupt the smooth muscle architecture resulting in necrosis of smooth muscle cells. Disrupted endothelial cell barriers allow the influx of erythrocytes into the subendothelium causing aneurysm and the development of thrombosis.

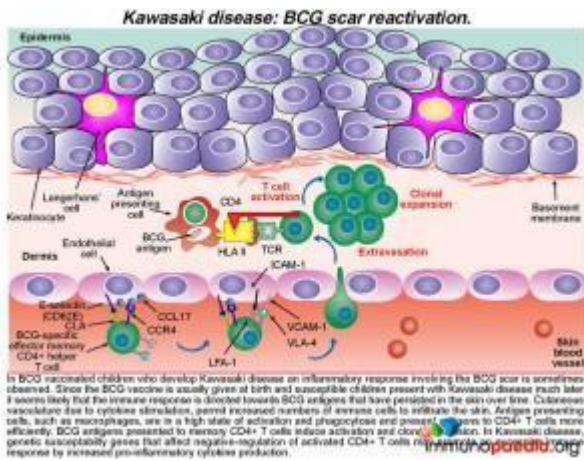
The exposed collagen activates platelets, which express CD40L(CD154). The engagement of CD40L with CD40 expressed by endothelial cells results in platelets secreting IL-1 and soluble CD40L. The release of both these solutes causes further activation of endothelial cells and severe inflammation. At the same time activated fibroblasts secrete extracellular

matrix proteins, such as collagen, that promotes scarring which results in vessel stiffness. When this occurs in coronary arteries, the damage may contribute to heart disease.



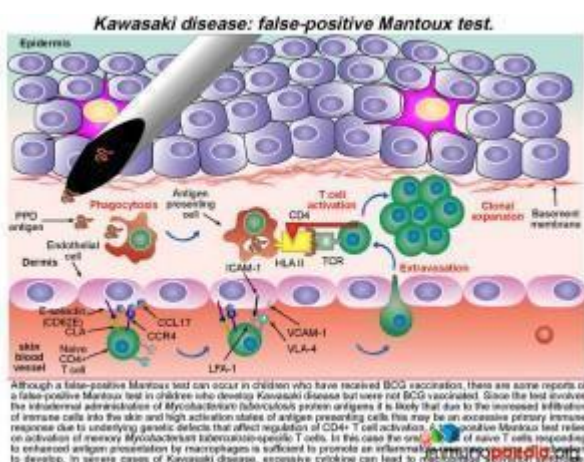
What leads to skin inflammation?

Alongside the well-documented vasculitis, skin inflammation is also often observed in patients with KD. This is seen predominantly as a polymorphous skin rash and is one of the diagnostic criteria for the disease. It is likely that the generalized skin involvement is a consequence of increased infiltration of immune cells through activated endothelium of cutaneous blood vessels into the dermis where an immune response to skin antigens can be mounted. This inflammatory response is excessive due to the dysregulation of CD4+ T cells, probably leading to a predominance of Th17 cells, and the high activation state of antigen-presenting cells. It has been noted that in regions where BCG vaccination is in use, up to a third of patients who succumb to KD also have a reactivation of their BCG scar, along with the usual skin rash.



What is the association between Kawasaki disease and BCG scar reactivation?

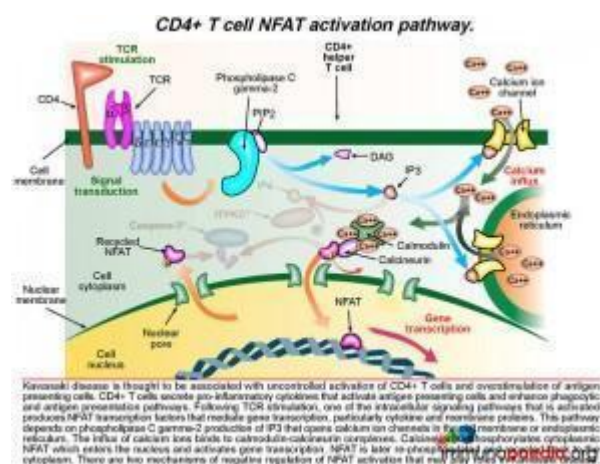
Since BCG vaccination is usually given at birth and susceptible children show clinical evidence of KD months to years later, it seems likely that the immune response is directed towards antigens present in the vaccine that have persisted in the skin over time. Due to cytokine stimulation, increased numbers of T cells and antigen presenting cells infiltrate the skin (via cutaneous blood vessels) and memory BCG-specific CD4+ T cells become re-activated and clonally expand in numbers. In KD, genetic susceptibility genes that affect negative-regulation of activated CD4+ T cells may promote an excessive immune response by increased pro-inflammatory cytokine production.



In our case study, the patient had both a reactivation of his BCG scar and a (presumed) false positive Mantoux test. While

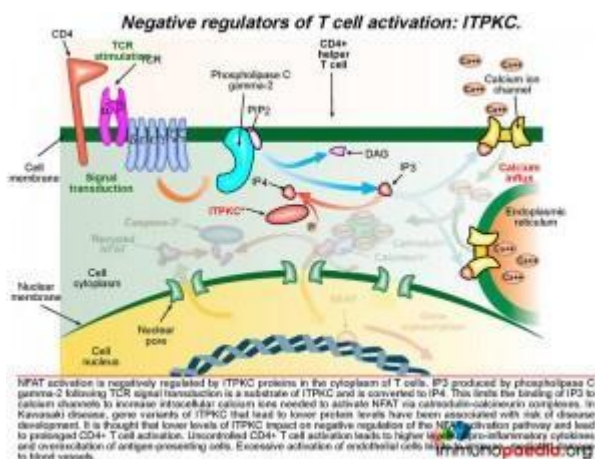
it is well recognized that children who have received BCG vaccination can sometimes have a false-positive Mantoux test due to cross-reactive immune responses to *Mycobacterium tuberculosis* antigens, there are also some reports of a false-positive Mantoux test in children with KD who were never BCG vaccinated. The Mantoux test involves intradermal administration of *Mycobacterium tuberculosis* protein antigens. It is likely that a combination of underlying genetic defects that affect negative regulation of CD4+ T cells, an increased infiltration of CD4+ T cells into the skin and the high activation state of antigen presenting cells all lead to an excessive localized immune response in patients with KD. A true-positive Mantoux test relies on activation of memory *Mycobacterium tuberculosis*-specific T cells, but in this case, a small pool of naïve CD4+ T cells responding to enhanced antigen presentation may be sufficient to promote an inflammatory response causing an induration to develop. In severe cases of KD, macrophage activation syndrome may even be present, due to the highly-activated state of macrophages.

Along with the immune mediated causes for Kawasaki Disease, as discussed, we will also discuss how a genetic predisposition in the patient together with immune dysregulation plays an important role in susceptibility to KD. We explain this using our graphics below.



A detailed look at CD4+ T cell NFAT activation pathway

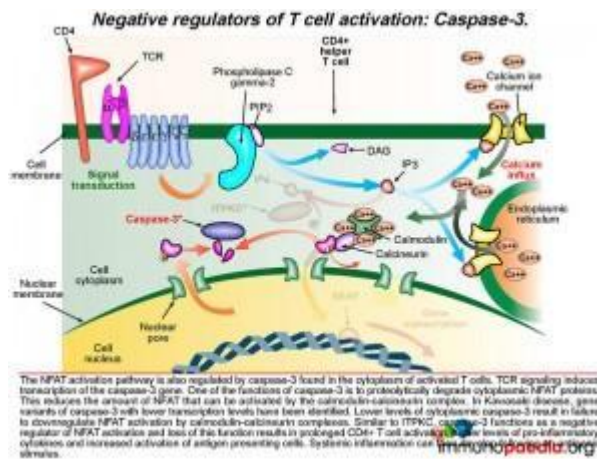
As discussed above, KD is associated with uncontrolled activation of CD4+ T cells and over-stimulation of antigen presenting cells. Following T cell receptor (TCR) stimulation after engagement with the MHC class II-peptide complex on the surface of macrophages, one of the intracellular signaling pathways that is activated results in the translocation to the nucleus of NFAT transcription factors that mediate gene transcription. This pathway depends on phospholipase C gamma-2 production of IP3 that opens calcium ion channels in the cell membrane or in the endoplasmic reticulum. Calcium ions bind to calmodulin-calcineurin complexes. Calcineurin dephosphorylates cytoplasmic NFAT, which enters the nucleus and activates gene transcription, such as cytokines and membrane proteins. NFAT is later re-phosphorylated and recycled back to the cytoplasm. There are two mechanisms of negative regulation of NFAT activation that may play a role in Kawasaki disease.



1) Negative regulators of T cell activation: ITPKC

NFAT activation is negatively regulated by ITPKC proteins in the cytoplasm of T cells. IP₃ produced by phospholipase C gamma-2 following TCR signal transduction is a substrate of ITPKC and is converted to IP₄, which inactivates it. This limits the binding of IP₃ to calcium channels to increase intracellular calcium ions needed to activate NFAT via calcineurin-calcineurin complexes. In Kawasaki Disease, gene variants of ITPKC that lead to lower protein levels have been associated with risk of disease development. It is thought

that lower levels of ITPKC leads to longer persistence of IP₃ following TCR signaling and prolonged activation of NFAT. This results in **prolonged and uncontrolled** CD4⁺ T cell activation resulting in release of higher levels of pro-inflammatory cytokines and over-excitation of antigen-presenting cells. Excessive activation of endothelial cells leads to immune-mediated damage to blood vessels that have been described.



2) Negative regulators of T cell activation: Caspase-3

The NFAT activation pathway is also regulated by caspase-3 found in the cytoplasm of activated T cells. TCR signaling induces transcription of the caspase-3 gene. One of the functions of caspase-3 is to proteolytically degrade cytoplasmic NFAT proteins.

This reduces the amount of NFAT that can be activated by the calcineurin-calcineurin complex. In Kawasaki Disease, gene variants of caspase-3 have been associated with lower transcription levels. Lower levels of cytoplasmic caspase-3 activity leads to increased levels of cytoplasmic NFAT and prolonged CD4⁺ T cell activation, higher levels of pro-inflammatory cytokines and increased activation of antigen presenting cells. Systemic inflammation can then develop following an antigenic stimulus.

In summary

Although the aetiology of Kawasaki Disease remains largely undetermined, understanding the immunology and genetics behind the mechanisms leading to this condition have been identified and provides insights into our patient's presentation. Thus, in light of our better understanding of this disease it is most likely that this patient was in fact TB negative at presentation. However due to the high incidence of TB in this geographic location, along with his suspicious clinical and laboratory findings and positive Mantoux test, it remained prudent to provide standard TB medication to this patient.

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Treatment

Patient was treated for 6 months on standard TB treatment

Five days after starting TB treatment, the patient received the standard Kawasaki Disease regimen – 2g polygam, [paracetamol](#) and 50mg [aspirin](#) daily.

Polygam was not repeated.

Aspirin was continued at a lower dose, 20mg daily, and [ibuprofen](#) was given for pain until all symptoms resolved.

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Final Outcome

Skin rash and joint involvement resolved

At 3 months, echocardiogram was repeated and was normal

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Evaluation – Questions & answers

What was the final diagnosis?

Kawasaki Disease, causing a reactivation of the BCG scar, as a result of inflammation

What is the primary cause of long term morbidity and mortality in Kawasaki Disease?

Coronary artery aneurysms develop in 25% of untreated patients and Kawasaki Disease is the leading cause of acquired heart disease in the developed world. Coronary artery aneurysms may cause sudden death or myocardial infarction due to rupture or thrombosis. Treatment with IVIG decreases the incidence of giant aneurysms (>8mm) by 95% and overall incidence of aneurysms by 85%. These patients need careful follow up with echocardiograms to detect aneurysms.

Which cytokines are known to cause the prolonged fever present in Kawasaki disease?

Increased levels of IL-1, TNF- α and IL-6

What are thought to be the precipitating events of the medium vessel vasculitis seen in Kawasaki disease?

Kawasaki Disease is thought to develop in genetically susceptible individuals following an initial inflammatory response to an inhaled immunogenic agent. A primary response occurs in the mucosal lymphoid tissues by activation of T and B cells. Then via a translocation of the agent or transport of the agent via trafficking phagocytic cells, the agent enters the systemic circulation. A systemic immune response is then initiated which leads to uncontrolled systemic inflammation and immune-mediated damage of the blood vessels, resulting in vasculitis.

Which genetic variants are thought to play a role in susceptibility to Kawasaki Disease?

Genetic susceptibility in the development of Kawasaki disease

is thought to involve polymorphisms in two genes encoding the T cell regulatory proteins ITPKC and Caspase-3. Genetic variants in either of these regulatory proteins result in prolonged and uncontrolled CD4+ T cell activation with a corresponding release of high levels of pro-inflammatory cytokines and over-excitation of antigen-presenting cells.

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Multiple Choice Questions

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