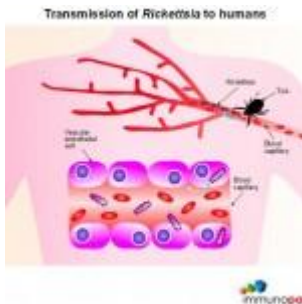


Case of sudden onset of fever, rash and neck pain



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Patient presentation

A previously healthy 6-year-old boy is brought to the emergency room with a 3-day history of fever, neck stiffness and a one day history of a generalised maculopapular rash.

Acknowledgement

This case study was kindly provided by Dr Monika Esser MMed Paed, Head of Division of Immunology, N.H.L.S Coastal Branch, Tygerberg Hospital.

History

A 6-year-old boy, previously healthy, presents with a 3-day history of progressively worsening fever, headache, neck stiffness and general malaise. In the last day he has developed a maculopapular rash which started on the extremities and is now also on the trunk. He has been complaining of nausea but no vomiting and his appetite has decreased.

Past medical and surgical history

No significant medical or surgical history. Road to health card shows all growth parameters to be within normal limits with all vaccinations up to date.

Family and social history

He lives with his mother, father, and one younger sibling who are all healthy. His mother was recently tested and is HIV negative. Father's status is unknown. They live on a farm in the Western Cape with a small number of livestock that includes cattle, sheep and goats.

Travel history

No travel outside of Western Cape in the last 12 months.

Differential diagnosis

- Meningitis
- Chicken Pox
- Tick Bite fever
- Measles
- Enteroviral infection

Examination

Vitals

- Pulse – 130

- Respiratory Rate – 34
- Temperature – 39.8

General

Inguinal lymph node enlargement

Chest

- Chest shape normal in appearance, tachypnoea present
- Midline trachea
- Clear on auscultation bilaterally

Cardiovascular

- Tachycardia with a regular rhythm
- Normal S1 and S2, no murmurs
- Bounding pulses felt radially and femorally
- Capillary refill within 2 seconds

Abdomen

- Normal on inspection.
- No rigidity or guarding.
- No organomegally
- Bowel sounds present

Neurological

Fully awake, alert and co operative

Dermatological

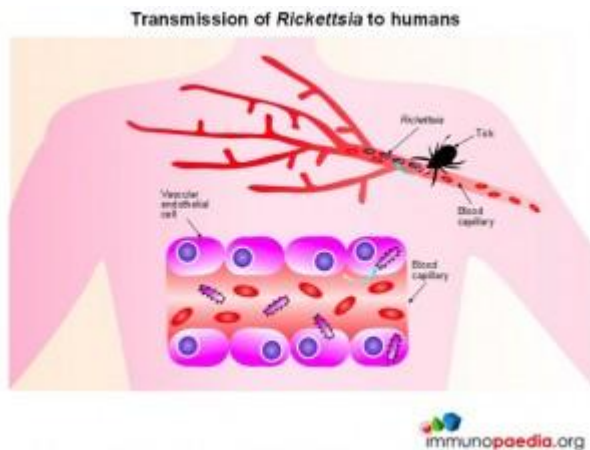
- Maculopapular rash with non-blanching petechial centers found in the lesions. Distribution is on arms, legs and trunk
- No bite marks or eschars seen

Investigations

Examination	Value	Normal Limits
WBC	8	(4-12 x 10 ⁹ /l)

Examination	Value	Normal Limits
HB	12	(12.1-15.2 g/l)
Platelets	222	(140-450 x 10 ⁹ /l)
C-reactive protein	50	(0-8 mg/l)
PCR – <i>R.conorii</i>	Negative	
Indirect immunofluorescence – <i>R.conorii</i>	Netavie	

Discussion

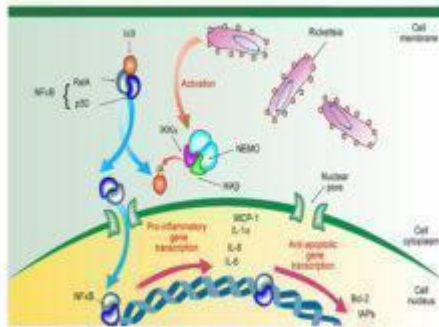


Rickettsial infection

Members of the *Rickettsia* genus are Gram negative, obligate, intracellular bacteria with a life cycle that involves both an arthropod vector and a vertebrate host. Mammals constitute the principle reservoir with humans considered incidental hosts. Humans become infected by Rickettsial bacteria by direct inoculation from infected ticks.

There are over 30 different Rickettsial species that are generally classified into 4 groups based on their biological, genetic and antigenic characteristics. The groups include the spotted fever group (SFG), typhus group, transitional group and ancestral group. The spotted fever group is of major importance and includes the highly pathogenic organisms *R.ricketsii*, which causes Rocky Mountain Spotted Fever, *R.conorii*, which causes Mediterranean spotted fever and *R.africae*, the causative organism of African tick-bite fever.

Previously *R.conorii* was thought to be the only cause of South African tick-bite fever however in 1992 *R.africae* was identified as an alternative cause.



Internalisation of spotted-fever group (SFG) Rickettsia leads to the activation of NF- κ B by activating the kinase activity of the NIK/IKK complex which phosphorylates the inhibitor molecule (I- κ B) bound to cytoplasmic NF- κ B. NF- κ B is a heterotrimer composed of p50 and p52 which is released from activated I- κ B and translocates to the nucleus. Gene transcription of pro-inflammatory cytokines such as IL-6 and IL-1 α and phospholipase D and BCP-1 is induced. Anti-apoptotic genes are also transcribed which promotes survival of Rickettsia bacteria within vascular endothelial cells.

Rickettsial Host Interactions

Following a tick bite which causes direct inoculation into the blood vessels, Rickettsial bacteria penetrate the vascular endothelial cells by a receptor-mediated endocytic pathway. Rickettsial bacteria express Outer membrane protein B (rOmpB)

which binds to host cell receptor Ku70 expressed on the surface of vascular endothelial cells. Via an enzymatic cascade, actin is polymerized which is necessary for the internalisation of the bacteria.

The cell membrane then invaginates and phagocytosis of the bacterium occurs resulting in a phagosome.

The cell membrane of the phagosome is lysed by the secretion of bacterial membranolytic proteins: phospholipase D and haemolysin C. This occurs before the phagosome fuses with a lysosome for degradation thereby permitting the bacteria to escape into the cytosol.

Movement within the cytosol is achieved by actin polymerisation at one of the poles of the bacterium due to the bacterial protein RickA. The actin filaments produced are long unbranched actin chains which grow and allow the bacteria to move through the cell. The bacteria are then also able to penetrate adjacent cells through plasma membranes.

Pathogenesis

The basic pathology of Rickettsial disease is that of a multi-organ vasculitic process that causes an increase in microvascular permeability. However, whole organ failure is uncommon because the vasculitis occurs focally.

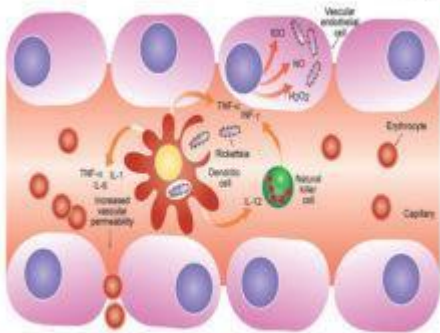
The bacteria also stimulate the major transcription factor NF- κ B in endothelial cells which induces pro-inflammatory

cytokine production, including IFN- γ , TNF- α , IL-1 β , IL-6 and IL-8. There is also inhibition of endothelial cell apoptosis leading to prolonging bacterial survival.

Haemostasis can also occur, which results in thrombocytopaenia. Endothelial injury can activate the coagulation cascade which will put the patient into a procoagulant state rarely resulting in DIC or haemorrhage.

Innate immune response to spotted-fever group (SFG) Rickettsia.

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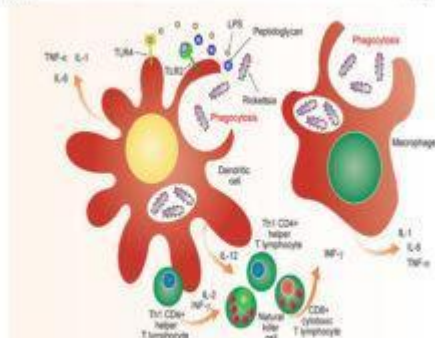
Initial innate immune responses to Rickettsia involve activation of natural killer cells by activated dendritic cells following engulfment of bacteria. They produce large quantities of IL-12 that stimulate natural killer cells to produce IFN- γ . Dendritic cells also produce TNF- α , IL-1 and IL-6 which cause fever and increase vascular permeability that can lead to skin rash formation. TNF- α and IFN- γ together induce endothelial cells to upregulate intracellular killing mechanisms such as nitric oxide (NO) and hydrogen peroxide (H₂O₂) production. Indoleamine-2,3-dioxygenase (IDO) synthesis leads to degradation of tryptophan needed by the bacteria to survive. These three mechanisms promote intracellular killing of bacteria.

Host defense and immunity

Initial innate immune responses to Rickettsia involve activation of natural killer cells by activated dendritic cells following engulfment of bacteria. They produce large quantities of IL-12 that stimulate natural killer cells

to produce IFN- γ . Therefore, during the early stages of infection, there are increased numbers of NK cells. The pro-inflammatory cytokines IFN- γ , TNF- α , IL-1 β and IL-6 cause fever and increased vascular permeability resulting in a maculopapular rash with non-blanching petechiae. The cytokines also activate the infected endothelial cells to kill Rickettsiae via two autophagic mechanisms – nitric oxide and hydrogen peroxide. A third mechanism is Indoleamine-2,3-dioxygenase (IDO) synthesis which leads to degradation of tryptophan needed by the bacteria to survive. The three mechanisms promote intracellular killing of bacteria.

Innate and cell-mediated immune responses to spotted-fever group (SFG) *Rickettsia*.



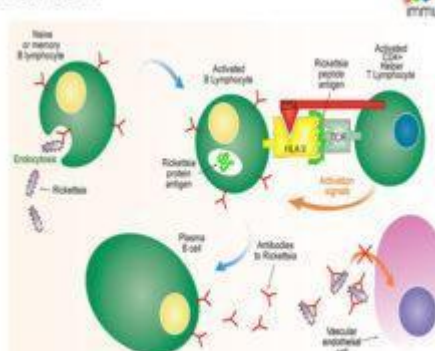
Clearance of *Rickettsia* is initiated by innate immune responses. Dendritic cells engulf free bacteria and are also activated by TLR4 binding to lipopolysaccharide (LPS) and TLR2 binding to peptidoglycan. Activated dendritic cells produce IL-12 that stimulates natural killer cells. They also secrete IL-1, IL-6 and TNF-α that cause fever, increase vascular permeability and stimulate liver production of acute-phase proteins. TNF-α and IFN-γ act on vascular endothelial cells to induce intracellular killing of bacteria. Antigen presentation to CD4⁺ helper T lymphocytes and IL-12 stimulation promotes a Th1 cell-mediated immune response that promotes CD8⁺ cytotoxic CD8⁺ lymphocyte killing of infected cells.

The clearance of *Rickettsia* is initially mediated by innate immune responses, where dendritic cells engulf free bacteria and also activate Toll Like Receptor (TLR) 4 with lipopolysaccharide (LPS). Activated dendritic cells then produce IL-12 that stimulates

natural killer cells. They also produce the above mentioned cytokines that cause fever, increase vascular permeability and stimulate liver production of acute-phase proteins especially by IL-6.

Humoral immunity forms late in the course of primary infection but confers immunity against re-infection.

Activation of B lymphocytes



Antibody response to cell surface antigens on *Rickettsia* bacteria, particularly rOmpB, prevent phagocytosis-mediated entry of bacteria into vascular endothelial cells. Opsonised bacteria are also detectable by phagocytes and natural killer cells expressing Fc receptors for IgG. IgM and IgG can activate the classical complement cascade. Anti-bacterial IgG is also used in the detection of *Rickettsia* infection by indirect immunofluorescence assay (IFA). Seroconversion occurs around 4 weeks after symptoms appear but antibodies may not develop if antibiotic treatment is initiated early.

Clinical manifestations of South African Tick bite fever

- Incubation period 5 – 7 days
- Fever, Malaise, Headache, Myalgia
- Eschar, an ulcerated lesion with central necrosis and surrounding inflammation
- Generalised maculopapular rash

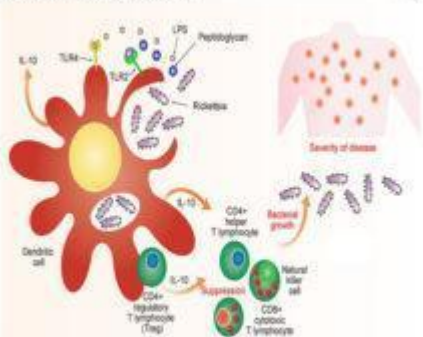
Occasionally infection with a SFG *Rickettsia* strain can lead to severe disease or even death. This is thought to be a

result of an imbalance between the pro-inflammatory responses that remove infecting bacteria and suppression of the immune response to avoid immune-mediated tissue damage. Suppression of cell-mediated immunity often occurs following excessive stimulation of TLR4 and TLR2 on dendritic cells which is thought to cause a switch from IL-12 to IL-10 production and ensuing immune suppression. Should this suppression occur before adequate clearance of bacteria is achieved, uncontrolled levels of bacterial growth may then lead to severe disease or death.

Possible suppression of immune responses to spotted-fever group (SFG) *Rickettsia* promotes severity of disease.

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Diagnosis



In some cases, infection with spotted-fever group (SFG) *Rickettsia* results in severe disease or even death. This is thought to be caused by an imbalance between pro-inflammatory responses that remove infecting bacteria and anti-inflammatory responses that reduce immune-mediated tissue damage. Suppression of cell-mediated immunity is mediated by IL-10 production by dendritic cells and CD4+ regulatory T lymphocytes (Treg). Excessive re-stimulation of dendritic cell TLR4 and TLR2 receptors by pathogen-derived lipopolysaccharide (LPS) and peptidoglycan can lead to a switch of pro-inflammatory cytokine production (IL-12) to anti-inflammatory cytokine production (IL-10). IL-10 stimulates Treg's and suppresses Th1 cell-mediated immune responses. Uncontrolled bacterial growth then leads to a more severe disease outcome.

- Clinical triad of fever, rash and an eschar in 50 – 75% of patients
- Confirmation of clinical diagnosis is usually delayed, therefore infections are typically treated empirically
- 3 Diagnostic tests are available- Serology, PCR techniques and Culture

Serology

- Most commonly used diagnostic tool.
- Immunofluorescence technique (IFA).
- Weil-Felix agglutination obsolete due to decreased sensitivity and specificity.
- Antigen derived from *R. rickettsii*
- Serology Pitfalls
- Cross reactivity within spotted fever group precludes speciation.

- Intra-group cross reactivity occurs at lower titers than group specific titers.
- Seroconversion occurs around 4 weeks after symptoms appear
- but antibodies may not develop if antibiotic treatment is initiated early. In this case the likely cause for the negative test results was that the patient was successfully treated with Doxycycline i.e. there was no antibody response due to early treatment administration.
- Some patients remain IgM positive for prolonged periods.
- Caution in interpreting positive IgM in the absence of positive IgG.
- Tests are not available for detection of *R. africae*, beware of false negatives

PCR

- Blood or skin biopsy (eschar).
- Rapid, sensitive and specific.
- Not freely available.

Culture

- Intracellular bacteria.
- Isolate on cell culture.
- Seldom used: Difficult & Hazardous.

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Treatment

- No large trials have been conducted to examine optimal treatment strategies
- Treatment of choice: Doxycycline 100mg 12hrly for 5 – 7 days (3 – 14 days)
- Patient should respond within 48 hours, otherwise reconsider the diagnosis
- Children/Pregnancy: Doxycycline for 48 hrs followed by macrolide.

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Final Outcome

The patient was diagnosed clinically with tick-bite fever (TBF) and was initially managed with Clarithromycin. This was later changed to Doxycycline with excellent response and the

patient made a full recovery.

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Evaluation – Questions & answers

What is the diagnosis?

Tick bite fever, causative organism *R. africae*

What receptors allow Rickettsial bacteria to attach to endothelial cells?

Rickettsial bacteria express Outer membrane protein B (rOmpB) which binds to host cell receptor Ku70 expressed on the surface of vascular endothelial cells

What process is needed for the bacteria to become internalised?

Actin is polymerised via an enzymatic cascade, which is necessary for the internalisation of the bacteria.

Once a phagosome enters the cell, how does it prevent degradation from fusing with a lysosome?

On entering the cell the phagosome is lysed by the bacterial membranolytic proteins phospholipase D and haemolysin C. This

permits the bacteria to escape into the cytosol.

How do bacteria move from cell to cell?

Actin filaments propel the bacterium through the cell and through adjacent plasma membranes.

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Multiple Choice Questions

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