CASE REPORT

Fever-triggered Brugada syndrome in an adult patient presenting with hemophagocytic syndrome induced by *Chlamydophila pneumoniae*

Miguel Bigotte Vieira,¹ Nuno Gaibino,² Alexandra Pignatelli,³ Anabela Oliveira²

¹Nephrology Department, Hospital Santa Maria—Centro Hospitalar Lisboa Norte, Lisbon, Portugal

²Internal Medicine Department, Hospital Santa Maria—Centro Hospitalar Lisboa Norte, Lisbon, Portugal

³Pathology Department, Hospital Santa Maria—Centro Hospitalar Lisboa Norte, Lisbon, Portugal

Correspondence to

Dr Miguel Bigotte Vieira, mbigottevieira@gmail.com

Accepted 23 September 2015

SUMMARY

A previously healthy 29-year-old man was admitted to our hospital, with a 4-day history of fever ($>39^{\circ}\text{C}$), rigours, diaphoresis, fatigue and retro-orbital headache. On examination, he was febrile (37.8°C) and tachycardic (110 bpm). Laboratory work up revealed bicytopenia (white cell count $1.37 \times 10^9/\text{L}$, platelets $60 \times 10^9/\text{L}$) and an increase in C reactive protein (9 mg/dL). The ECG showed ST segment elevation in V1, V2 and V3 leads. The patient was admitted and investigation was initiated revealing prolonged fever (>7 days), pancytopenia, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, elevated soluble CD25 and hemophagocytosis in bone marrow. Therefore, the patient presented 7 of the 8 diagnostic criteria of hemophagocytic syndrome. Laboratorial investigation for infectious causes was negative, except for IgA and IgG *Chlamydophila pneumoniae*. ECG re-evaluation on the day of discharge showed no ST segment elevation and no other abnormalities. Genetic testing for known mutations associated with hemophagocytic syndrome and Brugada syndrome did not show any mutations in these genes.

BACKGROUND

Although hemophagocytic syndrome and Brugada syndrome are not common, their occurrence is increasingly being recognised, as the recent published literature reveals. This article presents the case of a 29-year-old man who presented to the emergency room with complex systemic symptoms and a Brugada ECG pattern. After being admitted, investigations led to a complex final diagnosis of hemophagocytic syndrome triggered by *Chlamydophila pneumoniae*. It is worth noting that ECG changes disappeared with temperature normalisation and, as such, this patient presented a transient Brugada ECG pattern.

CASE PRESENTATION

A previously healthy 29-year-old man was admitted to our hospital, with a 4-day history of fever ($>39^{\circ}\text{C}$), rigours, diaphoresis, fatigue and retro-orbital headache. The patient had been seen at another hospital 17 days before, where he reported pleuritic pain. Laboratory work up, ECG and chest radiograph were unremarkable. The patient was discharged on analgesics and remained asymptomatic until the appearance of the described symptoms.

On examination, he was febrile (37.8°C) and tachycardic (110 bpm). Laboratory work up

revealed bicytopenia (white cell count $1.37 \times 10^9/\text{L}$, platelets $60 \times 10^9/\text{L}$) and an increase in C reactive protein (9 mg/dL (normal <0.1)). The ECG showed ST segment elevation in V1, V2 and V3 leads at a rate of 95 bpm (figure 1). The patient had no familial history of sudden death, had never experienced lipothymia or syncope and had a routine ECG performed 1 year prior, showing no abnormalities. Troponin, urinalysis and chest radiograph were normal. Urine and blood cultures were obtained and the patient was admitted to the general ward.

INVESTIGATIONS

During the first day (D1) in the ward, the ECG showed persisting ST segment elevation at a rate of 95 bpm. Echocardiographic evaluation revealed normal left ventricular function with no regional wall motion abnormalities. Brugada syndrome was considered and genetic testing (SCN5A sequencing) was requested.

Two days after admission, the patient was still febrile (38.5°C) and became icteric. The abdomen was distended, with no tenderness or guarding, and hepatosplenomegaly was present. He also developed a non-productive cough and bilateral basal crackles were present on auscultation. Blood analysis re-evaluation revealed anaemia de novo (10.9 g/dL), aggravating thrombocytopenia ($37 \times 10^9/\text{L}$) and leucopenia ($0.38 \times 10^9/\text{L}$) with absolute absence of neutrophils. Oxygen saturation was 97% on ambient air while chest radiograph presented clear lung fields and costophrenic angles of normal cardiac size and shape.

At this point, a bone marrow aspiration was performed. Granulocyte colony-stimulating growth factor (G-CSF) and broad-spectrum antibiotherapy with piperacillin/tazobactam plus amikacin were initiated.

In D6 to D8, the patient presented other de novo laboratorial abnormalities: ferritin was as high as 7405 ng/mL; tryglicerides were raised up to 510 mg/dL; liver enzymes and γ -glutamyl transferase (GGT) were persistently elevated (aspartate aminotransferase 526 U/L; alanine aminotransferase 737 U/L; GGT 333 U/L). Fibrinogen (118 mg/dL) and haptoglobin ($<7 \text{ mg/dL}$) were decreased.

As the bone marrow aspiration showed no infiltration by atypical cells, a bone marrow biopsy was performed.

An abdominal ultrasound detected homogeneous hepatomegaly with regular contours, gallbladder

CrossMark

To cite: Bigotte Vieira M, Gaibino N, Pignatelli A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208863

Figure 1 ECG showing ST segment elevation in V1, V2 and V3 leads at a rate of 95 bpm.

wall thickening without gallstones or sludge and no intra-hepatic or extra-hepatic biliary duct dilation. An enlarged spleen (maximum diameter 18 cm) with uniform echostructure was noted. Mild to moderate collection of intraperitoneal fluid was present as well as mild to moderate right pleural effusion.

A full body CT scan detected bilateral pleural effusion with partial atelectasis of the posterior segments of inferior lobes, a moderately enlarged liver (regular contours, homogeneous density, no focal lesions or biliary ducts ectasia) and an enlarged spleen with normal morphology. No enlarged lymph nodes were detected along the inferior vena cava, aorta and pelvic vessels.

In summary, the patient was a previously healthy 29-year-old man who had prolonged fever (>7 days), developed pancytopenia, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia.

Therefore, the patient presented five of the eight diagnostic criteria needed to establish the diagnosis of hemophagocytic syndrome based on the guidelines of the Histiocyte Society.¹ Genetic testing for known mutations associated with hemophagocytic syndrome (mutations in any one of PRF1, UNC13D (or MUN13-4), STX11 or STXBP2) was requested. A thorough investigation for primary and secondary causes was initiated.

Lupus anticoagulant, anticardiolipin, anti- β 2-glycoprotein I, antinuclear, anticitoplasmatic and antidouble-stranded DNA (dsDNA) antibodies were negative.

Serologies for parvovirus, cytomegalovirus, Epstein-Barr virus, paramyxovirus, coxsackievirus, adenovirus, HIV 1 and 2, C hepatitis virus, B hepatitis virus; *Coxiella burnetii*, legionella, *Bartonella*, *Brucella*, *Mycoplasma pneumoniae*, *Salmonella*, *Leptospira*, *Ehrlichia*, *Rickettsia conorii* and *Toxoplasma* were negative. Widal test for *Salmonella* and Bengal Rose reaction for *Brucella* were negative as were cytomegalovirus and Epstein-Barr DNA tests. *Influenza* nasopharyngeal swab was negative.

Natural killer (NK)-cell activity and soluble CD25 (α -chain of soluble interleukin (IL) 2 receptor) quantification in the blood were obtained. NK-cell activity was normal while soluble CD25 values were remarkably increased (12 433 pg/mL (458–1997 pg/mL)). High plasma concentrations of soluble CD25 (soluble IL2R α $\geq$ 2400 U/mL) supports the diagnosis, as it is one of the eight diagnostic criteria of hemophagocytic syndrome based on the guidelines of the Histiocyte Society.¹

The bone marrow biopsy was reviewed and the inexistence of abnormalities that have been described in hemophagocytic syndrome was confirmed. The bone marrow biopsy revealed

normocellular marrow with mature elements of the three haemopoietic series, a slightly decreased leukoerythroblastic ratio with mild left shift in the maturative range of white cells, an increased number of megakaryocytes, macrophages with hemophagocytosis and a mild increase in reticulin (figures 2–4).

A lumbar puncture revealed pleocytosis (30.0 cells/mm³). Glycorrachia and cerebrospinal total proteins were normal. Bacteriological, mycobacteriological and mycological evaluation were negative. Cytomegalovirus and Epstein-Barr DNA cerebrospinal fluid tests were negative. Cerebrospinal fluid changes have been described in >50% of patients with hemophagocytic syndrome, namely mild to moderate pleocytosis (with lymphocytes and macrophages predominant), elevated proteins, and/or hemophagocytosis.²

The imagiological findings observed in the abdominal ultrasound and in the full body CT scan have been previously described in hemophagocytic syndrome.³

DIFFERENTIAL DIAGNOSIS

The patient worked in a suburban area where numerous cases of Q fever had been reported, and presented with non-specific febrile illness, fatigue and headaches, which raised the suspicion of Q fever.^{4 5} Although the first serologies for Q fever were negative, it should be noted that seroconversion usually occurs during the first 2 weeks with 90% of patients having detectable antibodies by the third week of illness. According to the Centers for Disease Control and Prevention recommendations, laboratory confirmation of Q fever-suspected diagnosis should not delay the initiation of the first-line treatment option, doxycycline.

All the laboratorial investigations for infectious causes that had been initiated were negative, except IgA and IgG for *C. pneumoniae*, which is compatible with a recent infection by *C. pneumoniae*. Q fever and *C. pneumoniae* serologies were repeated 3 weeks later and the results were similar to the initial ones.

Our patient had fever, cough and bilateral basal crackles and showed clinical improvement when treatment with doxycycline was initiated, which supports the hypothesis that *C. pneumoniae* infection might have been the cause of the hemophagocytic syndrome.

TREATMENT

As an initial presumptive diagnosis of Q fever had been assumed, treatment had been initiated with doxycycline.

Figure 2 Bone marrow trephine biopsy section showing all three haemopoietic lineages. Paraffin embedded, H&E stain.

Figure 3 Bone marrow trephine biopsy section showing an increase in macrophages. Paraffin-embedded, immunoperoxidase, CD68.

Treatment was maintained after serologies results were obtained considering that doxycycline (100 mg orally two times a daily) for 10–14 days is also the treatment of choice for *C. pneumoniae*.^{6 7}

Taking into consideration that there had been partial recovery of neutrophil count, cultures had been negative and the patient had just completed 5 days of G-CSF administration, the broad-spectrum antibiotherapy with piperacillin/tazobactam plus amikacin was discontinued.

During the following 2 days, the patient started to improve. In order to suppress the life-threatening inflammatory process that underlies hemophagocytic lymphohistiocytosis (HLH), immunosuppressive treatment was initiated with 3-day pulse corticosteroid therapy, methylprednisolone and 5-day therapy with intravenous immunoglobulin followed by an 8-week tapering course of oral dexamethasone.

OUTCOME AND FOLLOW-UP

After the aetiological investigation had been concluded, we were convinced that *C. pneumoniae* infection was probably the trigger of the hemophagocytic syndrome in our patient.

During the following week, the patient presented remarkable clinical improvement with complete disappearance of his symptoms. At this point, laboratory abnormalities had already partly corrected. Haemogram, C reactive protein and fibrinogen had attained normal values while ferritin, triglycerides and hepatic enzymes were consistently approaching normal values.

Figure 4 Bone marrow trephine biopsy section showing neutrophils ingested by macrophages. Paraffin embedded, immunoperoxidase, CD68.

Figure 5 ECG showing no ST segment elevation at a rate of 47 bpm.

ECG re-evaluation on the day of discharge showed no ST segment elevation and no other abnormalities (figure 5). It is important to note that there were no ventricular arrhythmias identified in any of the ECG records of the patient. The patient was evaluated at arrhythmology consultation, and electrophysiological study or specific treatment were considered unrecommendable.

The patient completed an 8-week tapering dose of corticosteroid therapy with oral dexamethasone and returned to the hospital for a follow-up consultation, where resolution of the clinical and laboratory abnormalities were substantiated.

DISCUSSION

Yagi *et al*⁸ reported a case of a 3-year-old boy who presented with hemophagocytic syndrome triggered by *C. pneumoniae*. However, we did not find similar case reports in adults.

C. pneumoniae is an obligate intracellular bacterium. It is a cause of community-acquired pneumonia, pharyngitis, bronchitis, sinusitis, exacerbations of chronic bronchitis and asthma. It is estimated that *C. pneumoniae* infection is responsible for about 20% of lower respiratory tract infections. It has also been reported as a possible cause of atherosclerosis and central nervous system (CNS) disorders. Most infections caused by *C. pneumoniae* are usually mild, rarely running a severe course.^{6,7}

Hemophagocytic syndrome, also known as HLH, is a state of severe, life-threatening inflammation caused by an excessive, prolonged and ineffective immune response.⁹ Hemophagocytic syndrome has been classified according to the aetiology as either primary (ie, genetic) or acquired (ie, secondary to infections, malignancies or rheumatological disorders).

According to the diagnostic criteria used by the Histiocyte Society, the diagnosis of the syndrome is established when a patient presents at least five of the following eight criteria: fever $>38.5^{\circ}\text{C}$; splenomegaly; cytopenias (affecting at least 2 of 3 lineages in the peripheral blood); hypertriglyceridaemia (fasting $>265\text{ mg/dL}$) and/or hypofibrinogenemia ($<150\text{ mg/dL}$); hemophagocytosis in bone marrow, spleen, lymph nodes or liver; low or absent NK-cell activity; ferritin $>500\text{ ng/mL}$; elevated soluble CD25 (α -chain of soluble IL-2 receptor).² Our patient presented all the criteria with the exception of low or absent NK-cell activity. NK-cell activity is usually low or absent prior or during activation of hemophagocytic syndrome, as well as after remission following chemotherapy, in a significant proportion of patients, but normal or raised NK-cell activity has also been observed in some affected individuals, including those with UNC13D mutations.^{10,11}

Genetic testing for known mutations associated with hemophagocytic syndrome (mutations in any one of PRF1, UNC13D (or MUN13-4), STX11 or STXBP2) became available 3 months later and did not show any mutation in any of these genes. Brugada syndrome genetic testing (SCN5A sequencing) did not show any mutation in this gene.

The patient had presented a 'coved-type' Brugada pattern, which is characterised by the elevation of the ST segment descending with an upward convexity to an inverted T wave. This ECG pattern is typical in the classic Brugada type 1 and when, as in this case, the ST segment elevation is superior to 2 mm, it is diagnostic of Brugada syndrome. Brugada syndrome was identified in 1992, and is associated with high incidence of sudden death attributed to ventricular tachycardia or fibrillation. Its prevalence is estimated to be 5/10 000 and is thought to be responsible for 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts.¹² Mutations in the α -subunit of the cardiac sodium channel SCN5A account for 20% of cases.¹³

In some patients, the Brugada ECG pattern is transient and can only be revealed by triggers such as sodium channel blockers, antiarrhythmics, antianginals, vagotonics, psychotropic drugs or a febrile state, such as in our patient.¹³ A retrospective review of 111 patients with Brugada syndrome suggested that fever is a trigger for ECG changes and cardiac arrest. In the same study, the use of acetaminophen before admission appeared to reduce the risk of fever-triggered cardiac arrest. The authors recommend the use of antipyretics in patients with typical Brugada syndrome ECG changes during fever.¹⁴ Risk factors for sudden death have been identified including history of syncope and inducible sustained arrhythmias during programmed ventricular stimulation. Patients presenting these risk factors should undergo implantation of an automated cardioverter-defibrillator.¹⁵

We consider that fever, which was secondary to *C. pneumoniae* infection and hemophagocytic syndrome, may have triggered the Brugada ECG pattern in our patient. The treatment of *C. pneumoniae* infection and hemophagocytic syndrome subsequently led to fever resolution and normalisation of the ECG pattern.

Seventeen days before hospitalisation, the patient had been seen at another hospital where he had reported pleuritic pain. When specifically asked, our patient recalled he had already experienced similar thoracalgia in the past, during periods of great anxiety. It is possible that the referred pain was unrelated to the subsequent presentation.

Learning points

- ▶ Hemophagocytic syndrome, also known as hemophagocytic lymphohistiocytosis, is a state of severe, life-threatening inflammation caused by an excessive, prolonged and ineffective immune response.¹³
- ▶ Hemophagocytic syndrome has been classified according to the aetiology as primary (ie, genetic) or acquired (ie, secondary to infections, malignancies, or rheumatologic disorders).
- ▶ Brugada syndrome was defined as a clinical entity in 1992 and is characterised by three typical ECG patterns. In some patients, the pattern is transient and can only be revealed in the setting of a trigger, such as a febrile state.
- ▶ Brugada syndrome is thought to be responsible for 4% of all sudden deaths attributed to ventricular tachycardia or fibrillation in patients with structurally normal hearts.
- ▶ *Chlamydomphila pneumoniae*, which is estimated to be responsible for about 20% of lower respiratory tract infections, is a cause of community-acquired pneumonia, pharyngitis, bronchitis, sinusitis, exacerbations of chronic bronchitis and asthma.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Henter JJ, Horne A, Aricó M, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
- 2 Jordan MB, Allen CE, Weitzman S, *et al*. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;118:4041.
- 3 Fitzgerald NE, MacClain KL. Imaging characteristics of hemophagocytic lymphohistiocytosis. *Pediatr Radiol* 2003;33:392–401.
- 4 Marrie TJ. Q fever—a review. *Can Vet J* 1990;31:555–63.
- 5 Anderson A, Bijlmer H, Fournier PE, *et al*. Diagnosis and management of Q fever—United States, 2013: recommendations from CDC and the Q Fever Working Group. *MMWR Recomm Rep* 2013 Mar 29;62(RR-03):1–30.
- 6 Choroszy-Król I, Frej-Mądrzak M, Hober M, *et al*. Infections caused by *Chlamydomphila pneumoniae*. *Adv Clin Exp Med* 2014;23:123–6.
- 7 Blasi F, Tarsia P, Aliberti S. *Chlamydomphila pneumoniae*. *Clin Microbiol Infect* 2009;15:29–35.
- 8 Yagi K, Kano G, Shibata M, *et al*. *Chlamydomphila pneumoniae* infection-related hemophagocytic lymphohistiocytosis and acute encephalitis and poliomyelitis-like flaccid paralysis. *Pediatr Blood Cancer* 2011;56:853–5.
- 9 Malinowska I, Machaczka M, Popko K, *et al*. Hemophagocytic syndrome in children and adults. *Arch Immunol Ther Exp (Warsz)* 2014;62:385–94.
- 10 Ishii E, Ueda I, Shirakawa R, *et al*. Genetic subtypes of familial hemophagocytic lymphohistiocytosis: correlations with clinical features and cytotoxic T lymphocyte/natural killer cell functions. *Blood* 2005;105:3442–8.
- 11 Yamamoto K, Ishii E, Sako M, *et al*. Identification of novel MUNC13–4 mutations in familial haemophagocytic lymphohistiocytosis and functional analysis of MUNC13–4-deficient cytotoxic T lymphocytes. *J Med Genet* 2004;41:763–7.
- 12 Antzelevitch C, Brugada P, Borggreve M, *et al*. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;111:659.
- 13 Darbar D, Yang T, Churchwell K, *et al*. Unmasking of Brugada syndrome by lithium. *Circulation* 2005;112:1527–31.
- 14 Amin AS, Meregalli PG, Bardai A, *et al*. Fever increases the risk for cardiac arrest in the Brugada syndrome. *Ann Intern Med* 2008;149:216.
- 15 Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation* 2003;108:3092–6.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow