

Immune thrombocytopenic purpura as a complication of *Bartonella henselae* infection

La porpora trombocitopenica immune quale complicanza dell'infezione da *Bartonella henselae*

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INTRODUCTION

Bartonella henselae is a fastidious gram-negative organism, and it is the aetiologic agent for cat-scratch disease (CSD). This organism requires enriched blood media, with high levels of CO₂. That is why they are rarely cultivated routinely in most microbiology labs, and bacterial culture of blood or tissue samples is not the best diagnostic method for detecting these agents. Immunologic, histopathologic and PCR gene detection techniques can also lead to diagnosis, but none of these alternatives provide a diagnosis in all cases [1]. The clinical spectrum of bartonella infection has increased with the increasing number of studies concerning this genus. Besides the aforementioned diseases, we now know that the bartonellas can cause recurrent bacteraemia, endocarditis, and septicaemias, and are the cause of syndromes such as erythema multiforme, erythema nodosum, exanthemas, chronic adenopathy, and chronic fatigue syndrome. Osteolytic lesions, neurological and even psychiatric manifestations have also been associated with infections by these agents [2, 3]. Some of these manifestations may be fatal, especially in immunodeficient patients.

The organism is presumed to be carried by fleas, which then transmit it to cats, resulting in feline bacteraemia. A cat bite or scratch then transmits the organism to humans. Some recent studies have described a possible association between Henoch-Schonlein purpura (HSP), a

non-thrombocytopenic purpura, and seropositivity for *Bartonella henselae* (for example, a 2002 study from Florida demonstrated that 67% of patients with a recent diagnosis HSP had serologic evidence of infection with *Bartonella henselae* versus 14% of a control group), but in the literature only sporadic case reports have described a severe immune thrombocytopenic purpura (ITP) as a complication of *Bartonella henselae* infection [4-7]. We report a case of an immunocompetent child with recent *Bartonella henselae* infection presenting with purpura and thrombocytopenia and treated with intravenous immunoglobulin.

CASE REPORT

A nine-year-old child presented with a day history of purpura on his limbs and trunk. Eleven days before he presented fever (39°C) for three days, with a successive spontaneous regression, without use of medication, in association with cervical lymphadenopathy. He had no history of illnesses that would cause an immunodeficient state and he had no risk factors for infection with human immunodeficiency virus (HIV). On physical examination he had a temperature of 36°C, an extensive purpura over his limbs and trunk, a spleen palpable 1 cm below the costal margin and a cervical lymphadenopathy. There was no hepatomegaly. A laboratory test revealed a leukocyte count of 8.9×10^9 per litre (8,800 per μ l), with 0.24 neu-

trophilis, 0.63 lymphocytes, 0.06 monocytes, 0.04 eosinophils and 0.01 basophils. The haemoglobin level was 12.7 grams per dl and platelet count was 7×10^9 per litre (7,000 per μ l). Prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate (ESR) and reaction chain protein (RCP) were normal. Blood chemistry values were within normal values, with the exception of lactate dehydrogenase (472 U per litre, normal value 100 to 260). A chest roentgenogram and abdominal ultrasound examination were unremarkable, while neck ultrasound examination evidenced a diffuse cervical lymphadenopathy with reactive characteristics. Serological tests for *Brucella* species, *Salmonella typhi* and *paratyphi*, Epstein Barr virus, cytomegalovirus and *Toxoplasma gondii* were negative, as was hepatitis screening, including hepatitis A, B and C virus, auto-antibodies including antinuclear antibody, rheumatoid factor and anti-double stranded DNA. Analysis of sera for immunoglobulin (Ig) G antibodies to *Bartonella henselae* antigen was performed using an indirect immunofluorescence assay (IFA) method with positive and negative controls. A suspension of *Bartonella henselae* (ATCC 49882) in 0.1% saline was prepared with bacteria grown in-house on brain heart infusion agar supplemented with 5% sheep blood. The suspension was spotted onto 12-well slides (#ER-202W, Erie Scientific, USA) and air-dried for 1 hour. Slides were fixed in cold acetone for 15 minutes, air-dried and stored at -80°C . For initial screening, sera from controls and test subjects were diluted 1:32 in FTA Hemagglutination Buffer (Becton Dickinson, USA). A 1:32 dilution of goat anti-human IgG (whole molecule) FITC conjugated antiserum was used to detect IgG antibodies. Sera reactive at 1:32 were serially titrated two-fold to endpoint. A titre of 1:64 or higher was interpreted as evidence for infection at an undetermined time. A titre of 1:256 or higher was interpreted as evidence for recent infection. Our patient presented a titre of 1: 2048.

Treatment with intravenous gamma-globulin 1g/kg/die was started shortly after admission and was prolonged for two days. The two infusions of high-dose intravenous immunoglobulin produced a rapid response: 48 hours from the start of treatment the platelet count was 89×10^9 per litre with an initial reduction of purpura on limbs and trunk and on day seven the count was 179×10^9 per litre with a total regression of purpura. An antibiotic treatment with

azithromycin (15 mg/kg/die) was started and prolonged for 14 days, obtaining at the end of therapy a total regression of cervical lymphadenopathy. After 14 days from hospitalization the platelet count was 211×10^9 and the patient was asymptomatic, while the IgG titre was 1: 900. After one month the platelet count was 276×10^9 and IgG titre 1: 600.

DISCUSSION

Immune thrombocytopenic purpura is an infrequent yet well-recognized complication of viral infections such as mumps, rubella, varicella, cytomegalovirus, parvovirus and infectious mononucleosis by Epstein-Barr virus. However, it has rarely been reported as a complication of *Bartonella henselae* infection, although some reports have evidenced the association between HSP, a non-thrombocytopenic purpura, and bartonella infection [8]. We report a case of an immunocompetent child with clinical and serological evidence of *Bartonella henselae* infection presenting with purpura and cervical lymphadenopathy.

Because bartonella-induced thrombocytopenia has been reported so rarely in children, it is very difficult to know the mechanism by which bartonella induces the reduction in platelet count with diffuse purpura and the natural course of this disease. As regards the pathogenesis, two possible mechanisms have been proposed: a direct cytopathic effect of bartonella on megakaryocytes and an indirect, immune-mediated effect. The indirect effect is more likely to be responsible, given the temporal correlation between symptomatic thrombocytopenia and the onset of bartonella infection. In fact, purpura was observed eleven days after the onset of infection, characterized by insurgence of fever and cervical lymphadenopathy. This temporal relationship seems to show that an indirect mechanism is responsible for thrombocytopenia; a direct effect of bartonella would be expected to be evident much sooner in the clinical course.

The distinction between direct and indirect effect is fundamental because it may have very important therapeutic implications: the direct mechanism presupposes a good response to specific anti-bartonella antibiotic treatment (azithromycin), but the review of literature world-wide shows that treatment with azithromycin is of unproven efficacy, ranging

from no response to normal platelet counts [6, 7]. Indeed, in our case antibiotic treatment was started only to treat cat-scratch disease and not to obtain the regression of purpura. It is shown elsewhere that also corticosteroids are ineffective for regression of ITP [9].

Some recent case reports have recommended the use of intravenous immunoglobulin in cases of severe bleeding or evidence of purpura and petechiae or when the platelet level is very low (under 20×10^9 per litre). The use of high-dose intravenous gamma immunoglobulin (IVIG) for the treatment of ITP was first reported more than two decades ago. After the therapeutic benefit of IVIG was established in ITP, it was then successfully used to treat many other autoimmune diseases. Although a complete definition of the mechanism of IVIG action is still lacking, extensive research suggests that IVIG may achieve its therapeutic effects through multiple mechanisms. IVIG exerts immunomodulatory effects that may include anti-idiotypic neutralization of antiplatelet antibodies, stimulation of Fcγ receptor IIB expression, and inhibition of Fcγ receptor-mediated platelet destruction [10, 11].

Given the very low platelet count (7×10^9 per litre) our patient was treated shortly after admission with intravenous gamma-globulin 1g/kg/die for two days. In other case reports the patients were treated with gamma-globulin for only one day. We preferred two administrations in light of the very low platelet count. The response was very good with a complete regression of purpura on limbs and trunk and a rapid and persistent increase in the number of platelets.

In conclusion, this case report shows that *Bartonella henselae* must be considered a possible cause of ITP and IgG anti-bartonella must be determined in patients with thrombocytopenic purpura. Only intravenous immunoglobulin treatment is efficacious in bringing about a rapid and persistent increase in platelet count with regression of purpura, while, given the probable immune-mediated mechanism, antibiotic monotherapy is not effective for ITP regression.

Key words: bartonella, immune thrombocytopenic purpura, cat-scratch disease.

SUMMARY

Immune thrombocytopenic purpura is an infrequent yet well-recognized complication of viral infections, such as mumps, rubella, varicella, cytomegalovirus, parvovirus and infectious mononucleosis by Epstein-Barr virus. Some recent studies have described a possible association between Henoch-Schonlein purpura, a non-thrombocytopenic purpura, and seropositivity for *Bartonella henselae*, but in the literature only sporadic case re-

ports have described a severe immune thrombocytopenic purpura as a complication of *Bartonella henselae* infection. We report a case of an immunocompetent child with clinical and serological evidence of *Bartonella henselae* infection presenting with purpura and cervical lymphadenopathy and treated with intravenous immunoglobulin. The patient obtained a rapid and persistent increase in platelet count and a complete regression of purpura.

RIASSUNTO

La porpora trombocitopenica immune è una ben conosciuta complicanza di infezioni virali, come la rosolia, la varicella, l'infezione da cytomegalovirus o la mononucleosi. Alcuni recenti studi hanno evidenziato una possibile associazione fra la porpora di Schonlein-Henoch, non trombocitopenica, e la sieropositività per *Bartonella henselae*, ma in letteratura sono stati descritti sporadici casi inerenti ad una grave porpora trombocitopeni-

ca come complicanza dell'infezione da *Bartonella henselae*. Riportiamo un caso di un bambino immunocompetente con evidenza sia clinica che sierologica di infezione da *Bartonella henselae*, giunto alla nostra osservazione con porpora diffusa e linfadenopatia latero-cervicale e trattato con immunoglobuline per via endovenosa, ottenendo un rapido e persistente incremento delle piastrine con regressione della porpora.

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