



## Case report

## Atypical hemolytic uremic syndrome triggered by varicella infection



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## ABSTRACT

Varicella Zoster Virus (VZV) is a well-known virus that belongs to the *Herpesviridae* family which induces a self-limited disease except in specific cases in particular among stem cell transplant patients. This virus is not known however to trigger atypical Hemolytic Uremic Syndrome (aHUS). Here we report the case of a six-year-old boy who was hospitalized with fever and abdominal pains associated to pruritic and vesicular rash, thrombocytopenia and acute renal failure. He was diagnosed with aHUS precipitated by varicella virus. He was treated by an association of antimicrobials against potential superinfections, plasmapheresis and eculizumab for curative aHUS treatment. This was effective but after 6 months the kidney function remained poor.

The current case describes an aHUS associated to varicella infection as demonstrated by the simultaneous occurrence of the viral infection and aHUS manifestations. Apart from typical Hemolytic Uremic Syndrome which is triggered by bacteria mostly Shiga toxin producing *Echerichia coli* and *Streptococcus pneumoniae* or *Shigella*, aHUS may be linked to viral infections such as HIV, EBV and enteroviruses, but very rarely by varicella. This case highlights a possible even rare complication of varicella infection a very common childhood disease. This complication could be avoided by to anti-VZV vaccination.

## Introduction

Hemolytic Uremic Syndrome (HUS) is a type of thrombotic microangiopathy where mechanical hemolysis, thrombocytopenia and acute renal failure are the common manifestations [1]. Typical HUS caused by bacterial infections, mostly Shiga toxin producing *Echerichia coli* but also *Streptococcus pneumoniae* and *Shigella* [2] generally begins with bloody diarrhea. Atypical HUS (aHUS) occurs mainly in adults and in 5 to 10% of cases in children [3]. Apart from deficiencies of ADAMTS 13 or methyl malonic aciduria [4], the dysregulation of the alternative complement pathway is responsible of about 70% of aHUS [2]. Genetic abnormalities on genes controlling the complement alternative pathway are necessary but not sufficient to trigger the disease. In this specific context, the association with human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), or enteroviral infections [5] has been reported but only in three cases after varicella infection [6]. This report describes a case of aHUS that occurred after a varicella infection in a 6-year-old boy.

## Case report

The boy attended the emergency unit of the Val d'Ariege Hospital (France) presenting with fever and abdominal pain. The ultrasound showed splenomegaly and a hyperechogenic kidney. Elevated serum creatinine concentration (73  $\mu\text{mol/L}$ ), elevated protein reactive C concentration (91.8 mg/L) associated with anaemia (9.5 g/dL) thrombocytopenia (5 G/L) and schizocytosis (57/1000) were shown.

The patient was transferred to the pediatric unit of the Toulouse University Hospital. On hospital day 9, a pruritic and vesicular rash appeared with lesions in several stages of maturity leading to the diagnosis of varicella. On hospital days 23 and 25 varicella virus-DNA was detected in whole blood and in pleural fluid with an in-house real-time PCR targeting the DNA polymerase gene. At this moment the patient showed a renal impairment with a creatinine clearance of 63 mL/min/1.73 m<sup>2</sup>.

In order to discriminate between typical or atypical HUS, investigations on the mechanisms that could trigger the syndrome were conducted. Anti-LPS *E. coli* serology was negative on two samples at a two-week interval. The profiles of plasma amino acids and urinary organic acids were normal (homocysteine and vitamin B12). ADAMTS 13

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activity and C3, C4 and Complement Hemolytic 50 unit (CH50) levels were normal. Factor H and factor I rates were elevated (respectively 157% and 179%). No mutation for Membrane Cofactor Protein (MCP) was found excluding another type of aHUS. Anti-factor H antibodies were detected on hospital day 30. All the results were in accordance with an aHUS due to anti-factor H antibodies leading to the inhibition of the negative feedback on the complement alternative pathway.

On hospital day 9 acyclovir IV was initiated in association with antimicrobials (ceftriaxone, metronidazole and azythromycine) in order to prevent bacterial superinfection. Intravenous gamma globulin perfusion was used for the thrombocytopenia and eculizumab, a monoclonal antibody against C5 complement protein, was given twice at a one-week interval in association with plasma therapy followed by two cures of rituximab in order to treat the aHUS. Between hospital days 1 and 35 the level of anti-factor H antibodies remained elevated. No homozygous deletion of Complement Factor H-Related Genes (CFHR1 and CFHR3) was detected. On hospital day 80 mycophenolate mofetil was initiated in the long term. The patient was vaccinated against *Neisseria meningitidis* A, B, C, W135 and Y as eculizumab is well-known to increase the susceptibility to this micro-organism. Five months later no aHUS relapse but poor control of kidney function was shown. A new rituximab injection was planned for the future.

## Discussion

Varicella is a common self-limited childhood infection which is characterized by cutaneous lesions in several stages of maturity. This virus can induce auto-immune dysregulation (anti-protein S, anti-phospholipid) in patients with genetic susceptibilities [6]. However, the varicella virus is not commonly known to trigger aHUS (only 3 cases between 1980 and 2009) as compared to HIV, EBV, influenza A and enterovirus infections which can be more often associated. Many different drugs (quinine, cyclosporine and tacrolimus) or other situations (pregnancy, post-partum) can also trigger this disease [2]. Here we describe a case of aHUS that was triggered by the varicella infection as demonstrated by the simultaneous occurrence of the viral infection and aHUS. Clinical manifestations of the aHUS first day of hospitalisation (8 days before the vesicular onset that means during the two successive VZV viremias of the incubation period) and varicella DNAemia was still positive on hospital day 25.

Biological investigations showed anti-factor-H antibodies indicating a complement activity dysregulation. Factor H is the most important protein involved in the regulation of the alternative pathway which is constantly active and needs regulators (factor H, I and MCP). Antibodies against these factors inhibit the negative feedback of the complement activity therefore the alternative pathway is anarchically activated even in the absence of any contact with a pathogen. Anti-factor H antibodies are in most (90%) cases associated with CFHR1-CFHR3 homozygous deletion [7] that we did not detect in the current

case.

Eculizumab is an inhibitor of the alternative pathway that was approved by the Food and Drug Administration (United States of America) for the treatment of aHUS [8] in 2011 and became the new gold standard for this treatment as early initiation of therapy is associated with significant improvements in kidney disease outcomes [9].

Varicella infection is well known but the impact on natural human tolerance remains an enigma. In the current case the relationship between VZV infection and anti-factor-H antibodies appearance is not well understood. The way of how this virus impacts on human organism requires more research to know and better treat this pathology.

## Written informed consent

Written informed consent was obtained from the patient for publication of this case report.

## Conflicts of interest

None reported.

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