Severe Hemorrhage Secondary To IgA Vasculitis With Varicella Infection: A Case Report

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Case Report

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Abstract

IgA vasculitis (IgAV), formerly named as Henoch Schönlein Purpura, is an IgA-mediated systemic small vessel vasculitis with skin, gastrointestinal tract, joints, and kidneys involvement. It is the most common vasculitis in childhood. Varicella-zoster virus-associated IgA vasculitis has been reported previously in few cases. However, IgA vasculitis complicated by chickenpox rarely occurred severe hemorrhagic manifestation and had not yet been reported. Herein, we present a case of an eight-year-old girl who developed IgA vasculitis complicated by disseminated intravascular coagulation and multiple organ dysfunction syndrome, including severe acute pancreatitis and acute liver failure secondary to varicella-zoster virus infection and finally underwent blood purification including hemoperfusion, plasmapheresis, and continuous renal replacement therapy. Tumors and other diseases affecting coagulation and platelet function, such as systemic lupus erythematosus, ANCA-associated vasculitis, primary thrombocytopenia, and secondary thrombotic microangiopathies, have been excluded during her hospitalization. Varicella was considered to be the cause of the severe complications. A possible mechanism for the occurrence of severe complications is that chickenpox infection induces the production of heparin-like substances disturbing normal coagulation function, and finally occurs uncontrolled hemorrhage manifestation including gastrointestinal hemorrhage, uncontrolled bleeding at the catheter placement and injection site. She eventually was discharged after undergoing 37 days of treatment by antibiotics, antiviral drugs, protamine neutralizing heparin therapy and various blood products transfusion including platelets, red cells, fresh frozen plasma, cryoprecipitate, fibrinogen, and prothrombin complex transfusions. At the end of a month follow-up, the patient showed the purpuric rashes had nearly faded and had no sign of complication including the gastrointestinal tract, liver, and pancreas. Renal function tests and routine analysis of blood were normal. Hematuria(3+~4+) and proteinuria(1+~2+) can be seen in her urinalyses. At the 5th month follow-up, her renal function test and her urinalysis were normal, and her oral steroids were stopped completely. On this occasion, we should reduce the dose of heparin or no heparin in blood purification for IgA vasculitis complicated by chickenpox to reduce the incidence of severe bleeding or death.

Background

IgA vasculitis is a systemic, immune complex-mediated vasculitis and is the most common vasculitis in children. It characterizes palpable purple rash, arthritis, gastrointestinal and renal system involvement. IgA vasculitis is usually triggered by an antigenic stimulus including infectious agents, drugs, or food but is rarely triggered by varicella. Chickenpox has previously been reported to induce IgA vasculitis as a stimulant\(^1\)\(^–\)\(^5\). However, IgA vasculitis complicated by chickenpox rarely occurred severe bleeding and had not yet been reported. We report a case of IgA vasculitis occurring extremely severe hemorrhagic tendency dependent on transfusion of blood products complicated by varicella. Besides, the patient showed multiple organ functions were impaired with signs of skin damage, coagulation dysfunction, gastrointestinal, nephrotic, pancreatic, and hepatic involvement. Through literature review, these life-threatening complications have not all been described previously in the same patient.
Case Presentation

An eight-year-old girl previously in good health with no significant illness, was admitted to our department because of recurrent purpuric rashes, abdominal pain of 20 days’ duration. Twenty days before she admitted with palpable purple rashes, vomiting, and abdominal pain to another hospital. Typical purpuric rashes over her bilateral legs were described and her urine analysis was normal at the onset of the disease. Persistent hematuria and proteinuria were observed in her urinalysis since the 11th day of her hospitalization. The coagulation function test and the platelet count were with normal limits. Viral serology and renal biopsy were not performed in another hospital. She had been diagnosed with IgA vasculitis with nephritis and given intravenous glucocorticoid (1mg/kg.d) and hospitalized for 19 days in another hospital. Physical examination on admission to our hospital, the body temperature was 36.7°C, heart rate 85/min, respiratory rate 20/min, blood pressure 98/60mmHg. The lesions of purpuric rashes were initially predominantly observed on her bilateral legs (Figure A). The bilateral ankle joints were swollen. After admission, purpuric, herpes and crusted lesions were gradually extended over the whole body, including her face, trunk (Figure B), and legs. Laboratory examinations in our center showed lasting proteinuria and hematuria were observed in her urinalyses. The initial platelets count was 296・10^9/L (100-450・10^9/L). Renal function tests, initial coagulation function test, IgA, anti-nuclear antibody, anti-dsDNA, antcardiolipin antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) were within normal limits. The diagnosis of IgA vasculitis with nephritis was clear. Three days after admission, intravenous pulse methylprednisolone therapy (10mg/kg.d) was started for the first time because recurrent abdominal pain and rashes still existed after routine treatment. However, she underwent successively hemoperfusion (one time, the perfusion device was YTS-100, the blood pump speed was 80ml/min, unfractionated heparin (1mg/kg) was used for anticoagulation before procedures, the procedure lasted 2 hours) and plasmapheresis (one time, the perfusion device was TPE1000, the blood pump speed was 70ml/min, low molecular weight heparin (58IU/kg) was used for anticoagulation before procedures, the amount of plasma was 40ml/kg, the procedure lasted 1.5 hours) in our department because high-dose pulse hormone therapy was not effective, and she still suffered from progressive rashes and recurrent abdominal pain. Prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen before procedure were 13.1s(7.6-13.6s), 26.1s(16.9-36.9s), 184mg/dL(200-400mg/dL), respectively. PT, APTT, and fibrinogen after procedure were 18.1s, 66.9s, 147mg/dL, respectively. Four days after admission, she occurred specific infectious fever (the body temperature was 40.0°C) and spontaneously thrombocytopenia. The highest white blood cells count was 16.7・10^9/L (3.6-9.7・10^9/L), percentage of neutrophils was 90%(23.6-75%), the highest C-reactive protein (CRP) and serum procalcitonin were 41mg/L(0-8mg/L) and 3.72ng/ml(<0.05ng/ml), respectively. TORCH, EB virus, urine, stool, blood, and throat cultures were negative. Considering severe bacterial infection, she eventually had to receive antibiotics therapy such as ceftriaxone, imipenem, linezolid and tigecycline, and so on. Five days after admission, she occurred visible hematochezia, consequent uncontrolled bleeding at the catheter placement and injection site. The stool occult blood test was positive. The platelets count and hemoglobin level declined progressively (the lowest level were 12・10^9/L (100-450・10^9/L) and 40g/L(110-146g/L), respectively). ADAMTS13 activity was 73.8%(68-131%). Broken erythrocytes were never found in
peripheral blood. Haptoglobin and tumor markers tests were within limits. Lactate dehydrogenase level was 17529U/L(313-618U/L). During admission, her abdominal pain did not relieve completely, serum amylase and lipase were 271 units/L(30-110U/L) and 1958 units/L(23-300U/L), respectively. Abdominal computed tomography showed evidence of swelling of the pancreas and peritonitis. There was evidence of acute hepatic failure and disseminated intravascular coagulation (DIC) that alanine aminotransferase was 1967 units/L(9-52U/L), aspartate aminotransferase was 3010 units/L(14-36U/L), total bilirubin level was 132.2umol/L(3-22umol/L) and serum albumin level was 24g/L(35-50g/L). PT was prolonged(25.7 seconds, reference value 7.6-13.6s), APTT was prolonged (greater than 300 seconds, reference value 16.9-36.9s). Fibrinogen was significantly reduced(88mg/dl, reference value 200-400mg/dL) and d-dimers were elevated(173.35mg/l, reference value <0.55mg/L). She eventually stayed in the intensive care units(ICU) because of tachypnea, severe infection, uncontrolled bleeding, DIC and multiple organ dysfunction syndrome(MODS). She received continuous renal replacement therapy (two times, the treatment mode was CVVH, the filter was Paed, the blood pump speed was 60-100ml/min, replacement fluid rate was 700-1000ml/h, ultrafiltration rate was 0-100ml/h, heparin speed was 10-30iu/h, the procedure lasted 13-18h) and plasmapheresis(three times, the perfusion device was Fresenius P2, the blood pump speed was 60-100ml/min, the amount of plasma was 50ml/kg every time, the procedure lasted 2h). PT, APTT, and fibrinogen before procedure were 15.5s, 44.8s, 143mg/dL, respectively. PT, APTT, and fibrinogen after procedure were 12.5s, 49.7s, 114mg/dL, respectively. What's more, she received various blood products including platelets, red cells, fresh frozen plasma, cryoprecipitate, fibrinogen, and prothrombin complex transfusions due to coagulation dysfunction and constant bleeding. On the seventh day of admission, varicella virus nucleic acid was tested by fluorescence PCR, and the result was positive. Meanwhile, the anti-FXa activity's value was 3.1IU/ml(normal value was 0IU/ml, therapeutic concentration: UFH 0.3-0.6IU/ml LMWH 0.5-1.0 IU/ml). Combined with typical rash, she had been diagnosed as varicella, and started to reduce dose of intravenous methylprednisolone and given simultaneously acyclovir antiviral, intravenous immunoglobulin(the cumulative dosage was 57.5g), and protamine therapy. She eventually was discharged after undergoing 37 days of treatment by antibiotics, antiviral drugs, protamine neutralizing heparin therapy and various blood products transfusion. At the end of a month follow-up, the patient showed the purpuric rashes had nearly faded and had no sign of complication including the gastrointestinal tract, liver, and pancreas. Renal function tests and routine analysis of blood were normal. Hematuria(3+~4+) and proteinuria(1+~2+) can be seen in her urinalyses. At the 5th month follow-up, her renal function test and her urinalysis were normal, and her oral steroids were stopped completely. The timeline with relevant data from the event was listed in Figure C.

Discussion

Chickenpox is a common, self-limited contagious disease. However, certain rare but potentially life-threatening complications such as severe hemorrhage can be associated with the disease and are more likely to occur in the immunocompromised. IgA vasculitis is a small systemic vasculitis. Corticosteroids are one of the mainstays of treatment for IgA vasculitis. According to literature review, varicella-zoster virus associated IgA vasculitis is a rare condition reported previously3–7. Varicella was considered as a
stimulus that could trigger IgA vasculitis in most of these cases. Varicella antigens-induced immune complexes may promote the vasculitic process for IgA vasculitis\(^5\). However, IgA vasculitis complicated by varicella is sporadic and reported in few cases. The possible mechanism of IgA vasculitis complicated by varicella is that high-dose corticosteroid therapy for IgA vasculitis causes depression of serum IgG and specific antibodies resulting in reinfection or reactivation of varicella. IgA vasculitis was treated with high-dose corticosteroids before the onset of varicella in our case. The possible mechanism mentioned above may explain our issue.

Her coagulation function for this patient was normal on admission, and she had no signs of bleeding in other parts except skin ecchymosis when she did not suffer from varicella at the early stage. When accompanied by chickenpox, the platelets count declined progressively and DIC was evident with the evidence for progressive reduction of platelets, decreasing fibrinogen, prolonged APTT and elevated D-dimer. Tumors and other diseases affecting coagulation and platelet function, such as systemic lupus erythematosus(SLE), ANCA-associated vasculitis and primary thrombocytopenia, have been excluded. Some reports related to varicella were well-documented cases of DIC\(^8\)–\(^9\). Some are simple cases of postinfection thrombocytopenia\(^8\)–\(^10\)\(^,\)\(^11\). Both John D and Jairo Lizarazo reported a case of varicella with thrombocytopenia causing intracerebral hemorrhage\(^11\)\(^,\)\(^12\). Varicella is frequently accompanied by some degree of DIC. Bravo et al. found that chickenpox occasionally produces autoantibodies that target proteins involved in different stages of coagulation (lupus anticoagulants, antiphospholipid, and antiC, S, prothrombin, and antithrombin)\(^13\). Some studies showed that transient protein S deficiency caused by autoantibodies during varicella infection activates blood clotting, leading to wasting coagulopathy\(^14\). However, we detected that the child’s autoantibodies and anticardiolipin antibodies were negative. Therefore, we believe that there may be other mechanisms for the abnormal coagulation function of varicella following IgA vasculitis for this child.

It should be noted that the infusion of fresh frozen plasma, fibrinogen, and prothrombin complex in the treatment of DIC in our case is not effective, while the protamine treatment is effective. Therefore, we believe that IgA vasculitis complicated by chickenpox may induce heparin-like substances. The measurement of plasma anti-FXa activity indicates a significant increase, which also confirms our speculation. Heparin is the most widely used clinical anticoagulant. It was first discovered in the liver, hence the name heparin. It is an acidic mucopolysaccharide with a negative charge and a molecular weight ranging from 5 to 30kDa. In the body, it is mainly biosynthesized and stored by mast cells and basophils. It also exists in tissues such as lungs, blood vessel walls, intestinal mucosa, and almost all tissues and organs contain trace amounts of heparin. It is a natural anticoagulant in the body. Heparin carries a risk of excessive bleeding complications because of its anticoagulant activity\(^15\)–\(^17\). Plasma heparin quantitation is also known as the determination of anti-FXa activity. The heparin content in normal blood is relatively low (anti-FXa is <0.1U/ml), and the increased anti-FXa activity suggests the presence of heparin-like anticoagulants\(^17\)–\(^19\). The heparin-like substance is a chemical structure similar to heparin. It has the physical and chemical properties of glucosamine, accelerating the inactivation of multiple coagulation factors by antithrombin. Heparin-like substances are more common in patients with
SLE, liver disease, acute leukemia, malignant tumors, DIC, after organ transplantation, and taking certain drugs\textsuperscript{20,21}. When the liver is severely injured, the degradation of heparin-like substances in the liver is weakened. The release of glucosamine from vascular endothelial cells accelerates the inactivation of FⅡa, FXa, FⅫa, thrombin, and other coagulation factors. In addition, the activation of the fibrinolytic system by heparin-like substances aggravates the anticoagulant state of the blood. Patients may have ecchymosis, mucosal hemorrhage, hematuria, gastrointestinal bleeding, and bleeding at the injection site and wound. Heparin-like substances lead to prolongation of APTT, PT, TT, and cannot be corrected by ordinary plasma infusion in such patients\textsuperscript{22}. The above studies are consistent with the clinical manifestations of child we reported, supporting the speculation that IgA vasculitis complicated by chickenpox may induce heparin-like substances. When a patient with IgA vasculitis combined with viral infectious diseases has a severe bleeding tendency, and the effect of plasma infusion is poor. We need to be alert to heparin-like substances, which can be tested heparin concentration or TT correction test (protamine or toluidine blue) to identify, and recommend protamine treatment. As the patient had anemia, thrombocytopenia, renal involvement and other manifestations, increased LDH, we should be alert to the occurrence of secondary thrombotic microangiopathies. However, the evidence of thrombotic microangiopathies was insufficient because broken erythrocytes were never found in peripheral blood. ADAMTS13 antibody, haptoglobin and tumor markers tests were within limits. Autoantibodies, ACA and ANCA were negative. For the causes of thrombocytopenia, some thought that direct interaction between the virus and platelets resulted in early removal of platelets by the reticuloendothelial system. Another suggested that the release of neuraminidase from the virus attacked sialic acid in the platelet membrane and resulted in its destruction. We believe that DIC in our case was mainly caused by chickenpox infection, but the evidence of bacterial infections such as elevated CRP and calcitonin were found in the child, so we cannot rule out that bacterial infections may also play a role in the occurrence of DIC.

**Conclusions**

Possible mechanisms for the occurrence of severe complications for IgA vasculitis complicated by varicella are that chickenpox as a trigger may induce production of heparin-like substances in sera distorting normal coagulation function and finally occur uncontrolled hemorrhage manifestation. Therefore, we should reduce the dose of heparin or no heparin in blood purification for patients with IgA vasculitis complicated by chickenpox to reduce the incidence of severe bleeding or death. However, our study existed some limitations. Firstly, we did not carry out a renal biopsy to further know whether there was a microvascular thrombus in the kidney. Secondly, we did not further examine platelet function and the level of related factors such as protein S, protein C and other clotting factors. The specific mechanism of the above presentation still needs to be further confirmed.

**Abbreviations**

IgA vasculitis(IgAV); anti-neutrophil cytoplasmic antibodies(ANCA); prothrombin time(PT); activated partial thromboplastin time (APTT); C-reactive protein(CRP); disseminated intravascular coagulation(DIC);
intensive care units (ICU); multiple organ dysfunction syndrome (MODS); systemic lupus erythematosus (SLE).

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Consent for publication was obtained from her parents.

**Data and materials availability statement**

All data generated or analysed during this study are included in this article.

**Conflict of Interest Statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Author Contributions**

JJ conceptualized and designed the study, collected and arranged clinical data, drafted the initial manuscript, and reviewed and revised the manuscript. KL designed the data collection instruments, collected and arranged clinical data and visualization. HG conceptualized and designed the study, coordinated and supervised data collection, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**Figures**

**Figure 1**

HSP patient with the lesion of purpuric rashes in her legs on admission.
Figure 2

Herpes on her back.
**Figure 3**

A figure showcasing the timeline with relevant data from the event.