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Case Report

Cytomegalovirus Induced Thrombocytopenia in an Immunocompetent Pediatric Patient

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Received: August 30, 2018; **Published:** September 28, 2018

Abstract

In immunocompetent children, an acquired CMV infection is usually asymptomatic. But when it does present with symptoms it mostly manifests in a mononucleosis-like picture with fever, fatigue, pharyngitis, and adenitis, which is usually self-limiting. More severe presentations like pneumonitis, encephalitis, thrombocytopenia, colitis and retinitis are often seen in immunocompromised children and congenital CMV infections. Thrombocytopenia associated with CMV infection has been reported in around 25 cases in the literature in immunocompetent hosts, and only few of these reports were in the pediatric age group. Most of the reported case were treated with corticosteroids, and IV immunoglobulins while few discussed the benefit of Ganciclovir use and one report discussed the use of thrombopoietin receptor agonist. Our case presents a healthy child with thrombocytopenia, purpura and mucosal bleeding, with positive CMV, treated with IV immunoglobulins.

Keywords: *Cytomegalovirus; Thrombocytopenia; Immunocompetent*

Introduction

In immunocompetent children, an acquired CMV infection is usually asymptomatic. But when it does present with symptoms it mostly manifests in a mononucleosis-like picture with fever, fatigue, pharyngitis, and adenitis, which is usually self-limiting. More severe presentations like pneumonitis, encephalitis, thrombocytopenia, colitis and retinitis are often seen in immunocompromised children and congenital CMV infections. Thrombocytopenia associated with CMV infection has been reported in around 25 cases in the literature in immunocompetent hosts, and only few of these reports were in the pediatric age group. Most of the reported case were treated with corticosteroids, and IV immunoglobulins while few discussed the benefit of Ganciclovir use and one report discussed the use of thrombopoietin receptor agonist. Our case presents a healthy child with thrombocytopenia, purpura and mucosal bleeding, with positive CMV, treated with IV immunoglobulins.

Case Report

A 7 and a half years old, previously healthy girl, presented with a 2 day history of petechia and purpura all over the body and 1 day history of profuse gingival bleeding. There was no history of fever or any other associated symptoms. On examination, the child was afebrile, and vitally stable, she had widespread petechia all over the body and purpura over the limbs, trunk and face. She had submucosal bruising over the gums without active bleeding. She had no palpable lymph nodes, and no hepatosplenomegaly. Her initial investigations showed WBC Count 7.3 10^3/uL (5.0 - 13.0), HGB 12.3 g/dL (11.5 - 14.5) and Platelet Count 4 10^3/uL (180 - 400), which later on the same day dropped further to 2 10^3/uL. Blood film was consistent with severe thrombocytopenia and reactive picture. Liver function test, erythrocyte sedimentation rate, prothrombin, partial thromboplastin time, bleeding time, and fibrinogen were normal. Lactate dehydrogenase was elevated 630 U/L (0 - 580) as well as the retic count 3.38% (0.8 - 2.0) while direct coombs test was negative. Her immunoglobulin A and G were within normal ranges but immunoglobulin M was slightly elevated IGM 2.14 g/L (0.46 - 1.97). Viral screen

including Parvovirus Ab, Epstein Barr virus Ab and Adenovirus Ab was negative. Cytomegalovirus IgG and IgM was positive indicated current CMV infection and Cytomegalovirus DNA PCR in blood was positive with 7500 copies/ml (lowest detection limit = 135 copies/ml). The child received a dose of 0.9 g/kg of IV immunoglobulin (20g IV over 12 hours) and then received a second dose of IV immunoglobulin on the next day. The child developed headache and vomiting during the 2nd infusion, for which a Brain CT was done and was normal. The IV immunoglobulin was continued thereafter at a slower rate without any complications. After the 2 doses of IV immunoglobulin platelet count showed some improvement and rapid transient increase to 15 10^3/uL (180 - 400). Platelet counts dropped again on same day to 8 10^3/uL (180 - 400), so she received platelet transfusion (250 ml) and her platelets were monitored. The child did not develop any new bleeding. The petechia and purpura started to resolve and she was discharged home with platelet of 13 10^3/uL (180 - 400). On follow up the child was asymptomatic, and her platelet counts were slowly and gradually improving. It was not until six weeks later when her platelets raised above 20 10^3/uL and that was corresponding to a significant drop in the CMV viral load to 500 copies/ml. It took more than 4 months for her platelet count to normalize which is thought to have also correspond to a further drop in the CMV viral laod which was unfortunately not followed up further in this case. After 10 months her platelet count stabilized at 291 10^3/uL. Table 1 summarizes our patient's Platelet count, CMV DNA viral load, CMV IgM at onset and follow up.

Time	Platelet count 10^3/uL	CMV DNA PCR - viral load copies/ml	CMV IgM
Onset	4	7500	Positive
3 days	8	-	-
10 days	11	-	-
2 weeks	14	Undetectable	-
4 weeks	18	-	-
6 weeks	37	500	Equivocal
2 months	42	-	-
4 months	138	-	-
10 months	291	-	-

Table 1: *Platelet count, CMV DNA viral load, CMV IgM at onset and follow up.*

Discussion

Our report presents a rare case of CMV infection in an immunocompetent child associated with thrombocytopenia and purpura. CMV in immunocompetent individuals presents most of the time with a self-limiting mononucleosis like picture. On the other hand, more severe presentations including hepatitis, severe interstitial pneumonitis, acute meningoencephalitis, ulcerative colitis, and CMV -related vasculitis, or even multiorgan involvement are evident but not widely discussed in the literature due to misdiagnosis, and lack of reporting [1,2]. The child in our report was treated with IV immunoglobulin for 2 days which showed initial rapid improvement in platelet counts. On follow up of the platelet count and CMV viral load of the patient, it was concluded that there is an inverse relationship between the platelet count and the viral load, this observation might help in giving us a clue about the mechanism of thrombocytopenia in CMV infections. It has been suggested that there are two mechanisms in which CMV causes thrombocytopenia either directly by targeting the megakaryocytes or indirectly by an immune-mediated effect [3]. The rapid response observed initially after the administration of IV immunoglobulin can be explained by the indirect immune- mediated pathogenesis, but this effect was rapid and short lived. Moreover, the platelet counts didn't normalize until after 4 months and until the CMV infection was resolved as reflected from the viral load, which suggests that the immune mediated effect is not the only contributing factor to the thrombocytopenia but there should be a direct effect by the CMV infection [4]. This raises another question about the potential benefits of using ganciclovir for treatment of severe CMV infections in immunocompetent

patients. Ganciclovir is a synthetic guanine derivative antiviral that inhibits the replication against cytomegalovirus that is currently licensed for use in children with congenital CMV infections and immunocompromised children with HIV or post-transplant patients, but the use in immunocompetent children is needs more research because the adverse effects of the medication including granulocytopenia, anemia and thrombocytopenia might outweigh its benefits [5]. It is suggested that the treatment should be aimed to treat the underlying cause of thrombocytopenia which is the CMV infection in this case and for this reason it is thought that steroid are not recommended as they might have an immunosuppressive effect which leads to worsening of the CMV infection and increasing the chance of significant bleeding and relapse [6,7]. A newer therapy has also been suggested for the use in cases that are refractory to corticosteroids and IV immunoglobulin, which is the thrombopoietin (TPO)-receptor agonists like eltrombopag [8]. It is hypothesized to act directly on the platelet production which supports the theory behind the direct mechanism of CMV infection in causing thrombocytopenia. Current data are not sufficient regarding the most effective treatment for CMV induced thrombocytopenia and other related complications in immunocompetent children, and more studies are needed because these severe manifestations are not as rare as it is presumed [9].

Conclusion

CMV induced thrombocytopenia can present in immunocompetent children, the initial presentation might be hard to differentiate from the immune thrombocytopenic purpura, since only platelets are affected and other cell lines are normal, and this is usually a diagnosis of exclusion. Therefore, in case of CMV suspension, it is recommended to do the CMV PCR, and initiate treatment to reduce the risk of life-threatening bleeding. IV immunoglobulins and steroids in addition to other therapies including ganciclovir and thrombopoietin receptor agonists have been discussed in the literature but further studies are needed. We think that reporting cases of CMV related severe multi-systemic manifestations in immunocompetent children can help us understand the pathogenesis of this infection and to study the best management options.

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Volume 17 Issue 10 October 2018