Management of Brucella-Induced Thrombocytopenic Purpura

Brusellaya Bağlı Trombositopenik Purpura

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Summary
Brucellar infections are still a major public health issue in Mediterranean countries. Brucellosis may cause hematological abnormalities, particularly cytopenias. Severe thrombocytopenia leading to mucosal bleeding and purpuric rash is relatively infrequent. We herewith present three patients who were admitted with mucosal bleeding and purpura, and were finally diagnosed as brucellosis. The severe isolated thrombocytopenia, purpuric rash and compatible bone marrow findings on admission suggested the presumed diagnosis of ITP in all cases. All three patients received different treatment regimens and finally recovered without complications. There is no consensus regarding the management of brucella-induced thrombocytopenic purpura in the literature. The hematological consequences of brucellosis should always be kept in mind in the differential diagnosis of isolated thrombocytopenia in endemic areas.
(J Pediatr Inf 2009; 3: 83-5)
Key words: IVIG, Brucella, Corticosteroid, Thrombocytopenia

Özet
Brusella enfeksiyonları Akdeniz ülkelerinde halen önemli bir halk sağlığı sorunudur. Brusellozis hematolojik anormalliklere, özellikle sitopenilere yol açabilir. Mukozal kanamaya ve purpurik döküntüye sebep olacak şekilde ciddi trombositopeni ise nadiren görülmektedir. Bu yazıda mukozal kanama ve purpura ile başvuran ancak sonrasında brusellozis tanısı konulan 3 hastamızı sunmak istedik. Tek başına olan ağır trombositopeni, purpurik döküntü ve uygun kemik iliği bulguları nedeniyle tüm vakalara öncelikle ITP tanısı konuldu. Her üç hasta farklı ilaç protokolleri ile tedavi edilmelerine rağmen komplikasyonsuz iyileştiler. Literatürde brusella enfeksiyonlarına bağlı trombositopenileri yaklaşım konusunda fikir birliği bulunmamaktadır. Endemik bölgelerde izole trombositopeninin ayırıcı tanısında brusella enfeksiyonları mutlaka araştırılmalıdır.
(Çocuk Enf Derg 2009; 3: 83-5)
Anahtar kelimeler: IVIG, brusella, kortikosteroid, trombositopeni

Geliş Tarihi: 20.10.2008
Kabul Tarihi: 26.11.2008

DİP NOT: *Bu çalışma sadece bir sayı yayınlanıp yayından kaldırılan, artık yayın hayatında bulunmayan ve indekslenmemiş olan bir lokal dergide yayınlanmıştır.*

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Introduction

Brucellosis constitutes a major health problem with a worldwide distribution, particularly in the Middle East and Mediterranean1. Brucella infections may be the cause of many hematological abnormalities, particularly cytopenias. Thrombocytopenia is not infrequently observed, but is rarely severe enough to cause mucosal bleeding or purpura (2).

Since the clinical manifestation of disease is extremely protean, the diagnosis can easily be overlooked (3). According to the literature, many brucella-induced isolated thrombocytopenia cases were initially diagnosed as ITP, and treated with either corticosteroids or intravenous immunoglobulin (IVIG) until the diagnosis was made. There is quite a varied literature on the use of IVIG or steroids in thrombocytopenia and brucellosis. Some articles report improvement of thrombocytopenia with these adjuvant therapy regimens, whereas others report none.

The etiology of thrombocytopenia in brucellosis still remains obscure. Multiple possible mechanisms were proposed (4,5); hemaphagocytosis, disseminated intravascular coagulation, direct damage of bacteria to platelets, bone marrow suppression, hypersplenism, and immune-mediated damage. Although this phenomenon is frequently attributed to bone marrow suppression, as Brucella

spp express an affinity for reticuloendothelial tissue, it is now accepted as having a multi-factorial etiology. The immunomodulatory and anti-inflammatory effects of both corticosteroid and IVIG therapy render them valuable agents in the treatment of Brucella-induced immune thrombocytopenia las in other autoimmune or inflammatory disorders (6).

We herewith present 3 cases with isolated severe thrombocytopenia who were admitted with mucosal bleeding and purpura, diagnosed initially as ITP, and underwent different treatment options until and after final diagnosis of Brucellosis.

Patients

Case1. The 16 year-old boy was admitted with the complaints of epistaxis and purpura. He had been complaining of malaise and arthralgia for the previous 10 days, but had no fever. Physical examination showed no pathology except widespread purpuric exanthemas. He had leucocytosis (24,000/mm^3) with lymphocyte predominance, and thrombocytopenia (1000/mm^3). Serum biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), bleeding time, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were within normal limits. Serologic tests for salmonellosis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis B (HBV) and C (HCV) were negative. Evaluation of bone marrow aspiration revealed normal cellular distribution and maturation, but an increased number of megakaryocytes. The patient was hospitalized with the presumed diagnosis of ITP, and received high-dose (30 mg/kg) methylprednisolone. The platelet number did not increase in the following days. His body temperature gradually increased at the end of the first week, and he experienced arthritis. The serum agglutinin test for Brucellosis was positive at 1/320 titer, and then blood culture grew *Brucella melitensis*. The platelet number increased gradually up to 182.000/mm^3 one month after initiation of rifampin and trimetophrim-sulfamethoxazole therapy with the resolution of symptoms.

Case 2. The 11 and a half year old girl was admitted with mucosal bleeding and widespread purpura. She complained of headache for one week, and had had gingival bleeding for the previous 4 days. On admission, she had 38^{o}C fever, a purpuric and ecchymotic rash particularly on herlower extremities, but no organomegaly or arthritis. Complete blood count showed isolated thrombocytopenia of 13,000/mm^3. She had mildly increased ESR and CRP values but normal bleeding time, PT and aPTT. Serologic tests for salmonellosis, EBV, CMV, rubella, HBV and HCV were negative. Bone marrow aspiration revealed normal cellular distribution and maturation, but an increased number of megakaryocytes. The patient was hospitalized with the presumed diagnosis of ITP, and received high-dose (30 mg/kg) methylprednisolone. The platelet number was 8,000/mm^3 on the third day. The persistence of subfebrile body temperature values (37.2-37.9^{o}C) necessitated a Wright test which was positive at 1/160 titer. Brucella spp was later isolated on blood culture. The steroid therapy was discontinued and rifampin, deoxycycline and IVIG (1 gr/kg/day for 2 consecutive days) was commenced. The patient's clinical symptoms subsided and platelet number reached 242.000/ mm^3 one week after changing the therapy.

Case 3. The eleven year-old male subject was admitted with the complaints of malaise and nausea of one week duration, and epistaxis, gingival bleeding and widespread discoloration of his body for the previous 3 days. He had no history of fever or arthralgia. Physical examination showed no pathology other than a disseminated purpuric rash on the lower extremities. Laboratory tests isolated thrombocytopenia 3.000/mm^3. He had normal CRP, ESR, bleeding time, PT and aPTT. Serologic tests for salmonellosis, EBV, CMV, rubella, HBV and HCV were negative. Bone marrow aspiration revealed normal cellular distrubution and maturation, but an increased number of megakaryocytes. The patient was hospitalized with the presumed diagnosis of ITP, and received IVIG (1 gr/kg/day for 2 consecutive days). The platelet number was 57,000/mm^3 on the third day. As he had experienced fever on the following day, Wright agglutination was studied and found to be positive at 1/640 titer. He was put on treatment with rifampin and deoxycycline on the 6th day. The blood culture later grew *Brucella spp*. The platelet number was 352.000/mm^3 on the fourth day of antibiotherapy.

Discussion

Thrombocytopenia, like other hematological complications of brucellosis, is generally mild and resolves gradually with antimicrobial treatment. It is well known that platelet recovery usually occurs within 2-3 weeks of initiating appropriate antibacterial therapy (7-9) as observed in our first case. This is the reason that adjuvant steroid or IVIG therapy is not indicated in the absence of severe clinical picture.

Although mild to moderate thrombocytopenia is relatively frequent, being reported in 8% of brucellosis cases (7), it is rarely severe enough to result in bleeding into vital sites. In an excellent literature review by Young et al (9); although the majority of the subjects with brucella-induced thrombocytopenic purpura had received appropriate antimicrobial regimen, 4 of them (10%) had died due to complications, particularly intracerebral hemorrhage. Seventy-two percent of the above described patients, aged between 2-77 years, had also used concommitant steroids for periods of up to 8 weeks. Therefore prompt recognition of this complication and aggressive therapy are essential, since the mortality associated with intracranial bleeding is reported to be high.

The IVIG therapy is a good choice if there is any risk of hemorrhage, as it improves the platelet count when combined with antibiotics within 48-72 hours, as observed in our last 2 subjects. Unlike the steroids, IVIG prevents hypersplenism, remove autoimmune antibodies cases, and neutralizes bacterial antigens as well (6). These additional actions might be the reason for the earlier effect of IVIG therapy. Another important fact is that IVIG does not alter bone marrow findings like corticosteroids. Thus it is a good treatment option in emergency cases when pediatric hematology consultation is not readily available, which is the case for most health-care centers in developing countries.

On the other hand, there are some papers reporting incidence of side effects of IVIGsuch as headache and fever as being as high as %75 (8). In addition, patients may develop meningeal irritation findings and transient hemiplegia. As a result, IVIG should be kept for high-risk patients to reduce the risk of serious hemorrhage, and for emergency cases in the absence of hematology consultation. Having said that, we should keep in mind that low dose IVIG (0.25 to 0.5 g/kg for two days) was recently reported to result in fewer side effects (10).

Bearing in mind the considerable expense of IVIG, another approach is to give corticosteroids because of the similarity between the pathogenesis of ITP and infection-induced, immune-mediated thrombocytopenia (2). A previous history of serious adverse effects with IVIG use, or physicians' concern about IVIG complications are other indications. Recently, the rationale regimen is short-term steroid therapy as recommended by Sevinc et al (1) and Gurkan et al (2) because the majority of patients would have responded within the first week of treatment. The first 2 subjects in this paper did not experience improvement in platelet number with steroids within 7 days until the diagnosis and appropriate antimicrobial therapy was undertaken. Unless there is a response to steroid treatment in 3-5 days, it is of no use to extend the treatment period, since corticosteroids have the potential of causing dissemination of infectious organisms, by means of immunosuppression, thereby causing serious septic complications.

ITP in children is usually a self limiting disorder of either sex between the ages of 2 and 10 years11. Mortality due to hemorrhage, particularly intracranial, is extremely rare in ITP (12). It is well known that childhood leukemia rarely presents with a low platelet count alone, but many specialists in daily practice, even in developed countries uch as the UK (13) and USA (14), are likely to examine marrow films first in case of steroid usage. Bone marrow examination is an invasive method but certainly should be performed in the presence of any doubt about the diagnosis. In brucella endemic countries, it seems rational to wait for the results of agglutination tests in the differential diagnosis of isolated, mild to moderate thrombocytopenia before performing a bone marrow aspiration, particularly for children over 10 years old.

All the treatments are associated with potentially serious side-effects, and it is vital to carefully consider the balance of risks. The important lesson to be highlighted in this paper is that brucellosis should be considered in endemic countries and rapid steps taken to examine this diagnosis before embarking on bone marrow examinations and ITP treatments. In cases of severe, life-threatening hemorrhage, IVIG might well be life-saving, since it improves the platelet count rapidly in brucella-induced thrombocytopenia. Further controlled studies should be carried out to determine the most effective regimen for management of this entity.

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