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Visceral varicella-zoster virus (VZV) infection as an underestimated differential diagnosis of acute abdomen in a patient after allogeneic hematopoietic stem cell transplantation



Półpasiec trzewny u pacjenta po allogenicznym przeszczepie komórek hematopoetycznych szpiku – niewzględniana przyczyna w diagnostyce różnicowej ostrego brzucha

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ABSTRACT

We report a case of 18-year-old male patient who 5.5 months after allogeneic hematopoietic stem cell transplant (HSCT) developed severe abdominal pain not responding to high dose of opioids. The pain was accompanied by gradually increasing activity of liver enzymes and bilirubin concentration. The patient had a history of acute GVHD and was on steroid taper. Importantly, he was also temporarily off standard acyclovir prophylaxis. Provisional diagnosis of acute cholecystitis was made, however, cholecystectomy did not improve patient's condition. Clinical picture of severe abdominal pain without clear surgical cause, resistant to high doses of opiates with increasing activity of liver enzymes was highly suspicious of visceral varicella zoster virus (VZV) reactivation. Immediate introduction of intravenous acyclovir led to full recovery and complete resolution of abdominal pain. We conclude that reactivation of latent VZV with absent or delayed occurrence of characteristic skin vesicles may still pose a diagnostic challenge resulting in delay of the proper diagnosis and start of life saving antiviral treatment. Severe intractable pain in HSCT recipients with increasing activity of liver enzymes should evoke high

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Słowa kluczowe:

- przeszczep komórek hematopoetycznych szpiku
- półpasiec trzewny
- zapalenie pęcherzyka żółciowego
- ostry brzuch
- choroba przeszczep-przeciwciała
- profilaktyka acyklowirem

index of suspicion of the possible disseminated VZV and impose start of empirical treatment with high dose acyclovir.

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Introduction

Primary varicella-zoster virus (VZV) infection causes varicella (chickenpox). VZV remains latent in dorsal root ganglia after recovery from acute illness. Zoster also known as shingles results from the reactivation of dormant VZV, which in immunocompetent individuals commonly begins with classical skin manifestation localized within a dermatomal region with potential subsequent cutaneous spread. VZV reactivation might be promoted by aging, stress and prolonged, deep immunosuppression that occurs in hematopoietic stem cell transplant (HSCT) recipients [1]. Among these patients several specific factors facilitate VZV reactivation such as total body irradiation (TBI) in the pretransplant conditioning [2–5] or presence of active graft versus host disease (GVHD) especially requiring treatment with high doses of corticosteroids [3, 6–13].

The most severe and life threatening complication of VZV reactivation in HSCT recipients with high morbidity and mortality rates, is an internal organs involvement which may precede or occur without any cutaneous eruptions [2, 14, 15]. Lack of typical skin rash with blisters may delay the proper diagnosis and thus might be life threatening. Here we report a case of 18-year-old male patient, who 5.5 months after allogeneic HSCT for B-cell acute lymphoblastic leukemia developed visceral VZV reactivation without any preceding skin lesions.

Case report

An 18-year-old male after unrelated allogeneic HSCT (day +172) with late onset GVHD involving skin and liver was admitted in March 2008 to the Department of Pediatrics, Hematology and Oncology at University Medical Center in Gdansk (not a transplant center) with a sudden 1-day history of severe progressive abdominal pain. The day before admission patient underwent regular control check-up and was discharged without any remarkable symptoms or complaints. Upon admission, patient was afebrile anicteric, had normal vital signs and complained of severe crampy pain in the epigastric/right hypochondriac region with a positive Murphy sign. The pain was localized, without any radiation, periodically excruciating and no stimuli exacerbated nor alleviated the pain. On palpation there was no rigidity or rebound tenderness, vivid peristalsis was audible, stools were normal, no hepatosplenomegaly was noted. Additionally characteristic GVHD skin and mucosa

lesions (stage 1) were present, however, without any skin eruptions. Laboratory tests revealed mild lymphocytopenia (0.81 G/l), with normal neutrophil (4.29 G/l) and monocytes (0.21 G/l) counts, thrombocytopenia (40 G/l) and mild anemia (hemoglobin of 114 g/l) with increased activity (200 IU/l) of gamma-glutamyl transpeptidase (GGTP; normal ranges (NR): 8–61 IU/l) and alanine aminotransferase (83 IU/l) (ALT, NR: 0–55 IU/l). Aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) activity were normal. Serum and urine amylase levels, serum bilirubin, creatinine, electrolytes, glucose and clotting screen remained within normal ranges. Mild elevation of C-reactive protein (CRP) 7.9 mg/l was noted. Early cytomegalovirus (CMV) antigen was absent; serology viral investigations for hepatitis B and C were negative. The results of directly performed abdominal ultrasound and plain film were unremarkable as well as computed tomography of the abdomen. Gastroscopy revealed mild mucosal inflammation without ulceration.

The patient was transplanted from matched unrelated donor for relapsed acute B-cell lymphoblastic leukemia. The patient VZV serostatus was positive – varicella at the age of 4. Conditioning regimen included total body irradiation combined with etoposide, anti-thymocyte globulin with standard methotrexate and cyclosporine GVHD prophylaxis. Post transplant course was complicated by mild cutaneous GVHD (stage 1, day +43) and late hepatic (stage 2, day +133) GVHD that required oral methylprednisolone (1 mg/kg/d). The patient responded to high dose of steroids – gradual decrease of bilirubin concentration and activity of hepatic enzymes was observed that allowed start of standard steroids taper. Standard prophylactic post-transplant oral acyclovir was suspended temporarily at that time (approximately 6 weeks before acute onset of abdominal symptoms) due to suspected renal and hepatic toxicities of concomitant medications.

The clinical picture was unclear therefore conservative palliative therapy with broad-spectrum antibiotics, intravenous fluids and intensive pain relief medications (opioids) was initiated. The patient did not improve. Repeated ultrasound of the abdomen on the fourth day of hospitalization showed broaden common bile duct of 7–10 mm diameter and hyperechogenic gallstone of 6–7 mm diameter at the border of the gallbladder neck and cystic duct with enhancement of intrahepatic bile ducts. Ultrasound findings were indicative for calculus cholecystitis. Therefore endoscopic retrograde cholangiopancreatography was performed and revealed mild distension of the cystic duct without visible gallstones. Subsequent abdominal ultrasound of the abdomen was

performed that showed broaden common bile duct of 9 mm, gallbladder with irregular thickening of the wall up to 13 mm and 2 gallstones of 9 and 6.5 mm diameter probably in cystic or common hepatic duct. At the same time CRP increased up to 102 mg/l, GGTP 643 IU/l, ALP 155 IU/l, total bilirubin 1.8 mg/dl (direct 1.2 mg/dl), ALT 358 IU/l, AST 286 IU/l, serum and urine amylase levels remained within normal ranges. Due to the deterioration of patient general condition and increasing severity of abdominal pain that required continuous opiates infusion, emergency open cholecystectomy was performed in suspicion of cholecystitis. At the surgical examination macroscopically acalculous, inflamed gallbladder was found with infiltration of hepatoduodenal ligament and dilatation of cystic duct up to 8 mm without gallstones. Histopathological examination was consistent with *cholecystitis chronica activa fibrosa*; no viral inclusions were found.

The following day after surgery – 8 days after admission, skin rash appeared at the trunk and epigastric region with gradual generalized spread over the upper part of the body. Consulted by telephone primary pediatric transplant center suggested flare of GVHD and recommended to increase methylprednisolone dose up to 2 mg/kg/d. Since the clinical picture was not completely consistent with GVHD exacerbation (intractable, excruciating with fast onset abdominal pain without any other concomitant GVHD symptoms is not a characteristic feature at the start of GVHD flare) a second opinion was asked from a local adult transplant specialist for whom the sequel of clinical symptoms was rather characteristic for visceral VZV reactivation than GVHD flare. Hence, immediate intravenous acyclovir therapy was added: 500 mg/m² every 8 h along with human varicella-zoster immunoglobulin administration. Next day after the start of antiviral therapy typical herpetic cutaneous vesicles appeared that indirectly confirmed VZV reactivation with preceding visceral involvement. Before acyclovir treatment hepatic enzymes reached the highest activity: GGTP 2184 IU/l, ALT 686 IU/l, AST 670 IU/l, while bilirubin level increased to 5.2 mg/dl; serum and urine amylase levels remained within normal ranges. Over the next days of acyclovir treatment activity of hepatic enzymes started to decline. However, the patient developed bilateral pneumonia with hypoxemia that was probably VZV related. Early CMV antigen was repeatedly absent although PCR testing for CMV was not available at our center at that time. In addition the patient was on continuous trimethoprim/sulfamethoxazole prophylaxis therefore *P. jiroveci pneumonia* was less likely. Fortunately within four next days of acyclovir treatment and after the patient's general condition improved, hypoxemia and abdominal pain resolved, skin lesions started to heal. After more than two weeks patient was switched to oral acyclovir and continued it without VZV relapse for the next twelve months. The patient is alive and in good condition, off immunosuppression at the time of manuscript preparation.

Discussion

Before introduction of routine antiviral prophylaxis post HSCT, VZV reinfection occurred in almost 50% of seropositive adult recipients [7, 16, 17]. Similarly, the incidence of

herpes zoster in VZV seropositive children following allo- and auto-HSCT was reported within the range of 23–67% [18–23]. In the era of posttransplant antiviral prophylaxis, VZV reactivation still occurs although at the significantly lower rates between 2.6% and 30% in the first year and 5% thereafter; VZV visceral reactivation without skin involvement in HSCT recipients is even less common [10, 24, 25].

VZV reactivation can present as localized zoster (shingles), or may cause end organ disease such as hepatic failure that might be fulminant and fatal [26], pneumonitis [27, 28] and pancreatitis [29, 30]. It may also cause gastric ulcers [31], intestine necrosis [32], paralytic ileus – Olgivie's syndrome [33], ulcerative oesophagitis, gastritis and duodenitis [34], acute glomerulonephritis [11, 12], disseminated intravascular coagulation [12, 26], urinary retention from sacral nerves VZV [35], meningoencephalitis [28, 36, 37]. VZV reactivation may start with visceral presentation, as in our case without preceding characteristic vesicular skin changes which causes considerable diagnostic difficulties [3, 6, 12, 15, 20, 26, 30, 38–41]. In immunocompromised patients it can be fulminant and fatal and the proper diagnosis might be made *post mortem* [6, 12, 26, 38–41].

The clinical picture of visceral VZV reactivation is rather characteristic. It usually presents as gradually but shortly developing severe abdominally localized pain in the upper right hypochondriac region indicating a need for surgical intervention and requiring opioids for treatment. The pain is mainly of neuropathic nature due to VZV-neuritis. Therefore may be responsive to antineuropathic agents but less likely to opioid therapy. If response to antineuropathic treatment is observed it might be helpful diagnostically as suggested by some reports [34, 38, 40, 42, 43].

Other less specific symptoms such as vomiting, nausea and diarrhea often accompany abdominal tenderness [3, 6, 27, 39]. In a group of 600 immunocompromised children, 31 developed varicella and almost 50% (15/31) of them had visceral involvement (hepatitis, pneumonitis), 11/15 had severe abdominal pain requiring opioids [44]. Our patient also developed bilateral pneumonia that was likely caused by VZV spread. Skin lesions may never appear or appear delayed. The delay from the first visceral symptoms to the vesicular rash occurrence may take 1–10 days in about 50% of patients [6, 14, 28–30, 34, 39]. In our patient it took 8 days. Spanish authors conclude their report of 4 cases of disseminated VZV that an abdominal severe pain of unknown origin in HSCT recipients should always be regarded as a possible prodromal phase of a disseminated VZV infection [39].

In addition to the pain the second characteristic feature of visceral VZV reactivation is increasing activity of liver enzymes: transaminases (ALT, AST) and GGTP that is accompanied by gradual rise in concentration of bilirubin. Other laboratory findings include increase of pancreatic enzymes activity. In our case the laboratory abnormalities in liver enzymes, although mild, concerned initially ALT and GGTP and later also AST and ALP activity. Pancreatic enzymes in our patient remained within normal ranges.

According to Doki et al. [6] visceral VZV infection could be established through histological examination of internal organ or viral culture made from it. At present, definite

diagnosis of visceral VZV reactivation in HSCT recipients could be made using PCR to detect VZV DNA in peripheral blood [15, 38, 45]. Unfortunately, at the time of hospitalization of our patient it was not available at our center (year 2008).

Difficulties in a proper diagnosis of visceral VZV reactivation without skin lesions may, as in our case, lead to unnecessary surgical interventions [29, 38, 40, 46]. In the absence of cutaneous manifestations, occasionally, laparotomy may help to establish correct diagnosis by revealing hemorrhagic spots on the internal organs [32, 38] or viral herpes inclusions at microscopic assessment of the affected tissues [40]. Unfortunately in our patient, the histopathological examination of inflamed gallbladder did not find pathognomonic viral inclusions.

In our patient cholecystitis was an initial provisional diagnosis. There are few similar reports of HSCT recipients with such provisional diagnosis who underwent surgical intervention and were finally diagnosed with visceral VZV [14, 26, 27, 40]. Severe abdominal pain with unsatisfactory response to opioids was a dominant clinical feature in all cases. Acute cholecystitis among adult HSCT recipients up to 100 days after transplantation, despite the etiology is a rare event – it has been reported in about 1–5% of patients [47, 48]. Interestingly, cholelithiasis was recognized through ultrasound examination in 8.5% (20) of 235 pediatric HSCT patients, in which three had symptoms of acute cholecystitis [49]. David et al. [27] in the group of 10 HSCT recipients with visceral VZV reported 6 patients in whom abdomen ultrasound disclosed biliary sludge in around 70%, solitary gallstone in 20% and 20% had biliary tract dilatation, no surgical interventions were undertaken. Additionally, computed tomography of the abdomen was done in 6 of these 10 patients which results were irrelevant as it was in our case.

Difficulties in the diagnostics led also to the suspicion of hepatic GVHD exacerbation in our patient. The increase in activity of liver enzymes and rise of bilirubin concentration could be consistent with this diagnosis, however, severe acute pain that occurred from the very beginning rather not. The decision to increase the dose of methylprednisolone could have fatal outcome in a patient with active VZV replication, as it is emphasized by other authors [27, 50].

The most important factor contributing to the reactivation of VZV in our case was discontinuation of acyclovir

prophylaxis at the time of the diagnosis of hepatic GVHD (day +133 post HSCT). This emphasizes the importance of current guidelines that recommend acyclovir (or valacyclovir) prophylaxis for the period of 1 year or even longer in the presence of immunosuppressive therapy and GVHD [10, 24, 51, 52]. Still, despite oral acyclovir prophylaxis, in a recent 2-year multicenter nationwide study within all recorded viral infections in allo-HSCT pediatric patients VZV stands for 2.6% [25]. The reactivation of VZV most commonly occurs 3–12 months after transplantation, but may reactivate considerably later which has to be kept in mind especially when acyclovir prophylaxis is stopped [2].

VZV IgG status documentation before transplantation is recommended for all HSCT recipients, since recommendation on the length of acyclovir treatment post transplant depends on the VZV serostatus of the recipient (Table 1) [10, 24]. VZV seronegative patients are at high risk for serious complications resulting from primary infection as well, and thus exposure should be prevented if at all possible. Although after bone marrow transplantation VZV infections are commonly reactivation of latent virus, primary infections occur as well and there have been reports of newly acquired varicella infections in VZV seropositive patients [53, 54]. Therefore eliminating or limiting the exposure of all HSCT recipients to varicella is recommended. For instance any child without a history of chickenpox who will be in direct contact with HSCT recipients should be vaccinated against VZV. If it develops varicella infection (chickenpox), it is recommended to treat the child with antivirals to reduce the period of contagion and the severity of potential exposure to the HSCT patient. The lesson from our case is that even temporary suspension of acyclovir may have fatal consequences for the patient and careful adherence to the anti-infective prophylaxis guidelines post HSCT should be kept. It is also necessary to continuously reevaluate indications for anti-infective prophylaxis in HSCT recipients and reintroduce beyond recommended time if needed in selected cases.

In summary, HSCT recipients with undetermined severe abdominal pain pose significant diagnostic and therapeutic challenge. Visceral VZV must be included as possible diagnosis, irrespective of acyclovir prophylaxis. Abdominal pain without clear surgical cause, resistant to high doses of opioids together with increasing activity of liver enzymes should alert physicians taking care of HSCT recipients of

Table 1 – VZV prophylaxis depends on the VZV serostatus of HSCT recipient

VZV recipient serostatus	Start of prophylaxis	Discontinuation of prophylaxis
<i>Allogeneic recipients</i>		
Positive, not vaccine induced	Start of conditioning	Day +365 or 6 months after immunosuppression ends
Positive, vaccine induced	Start of conditioning	Day +100
Negative	None	N/A
<i>Autologous recipients</i>		
Positive, not vaccine induced	Start of conditioning	Day +365
Positive, vaccine induced	Start of conditioning	Day +100
Negative	None	N/A
N/A, not applicable.		

rare but fatal, if not diagnosed on time, visceral VZV reactivation.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

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Ethics/Etyka

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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