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JOINT AND FASCIA MANIFESTATIONS IN THE COURSE OF GRAFT-VERSUS-HOST DISEASE (GVHD) AS A DIAGNOSTIC TRAIL FOR DOCTORS OF VARIOUS SPECIALTIES – CASE REPORT

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SUMMARY

Introduction

Patients who undergo successful allogeneic hematopoietic cell transplantation are exposed to numerous post-transplantation complications. The most severe is graft-versus-host disease (GVHD), which is diagnosed, according to various authors, in between 30–80% of cases. Among the often-overlooked tissues are joints, muscles, and fascia.

ZMIANY W OBRĘBIE STAWÓW I POWIĘZI W PRZEBIEGU CHOROBY PRZESZCZEP PRZECIWKO GOSPODARZOWI (GVHD) JAKO TROP DIAGNOSTYCZNY DLA LEKARZY RÓŻNYCH SPECJALNOŚCI – OPIS PRZYPADKU

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STRESZCZENIE

Wstęp

Pacjenci, u których z powodzeniem wykonano allogeniczną transplantację komórek krwiotwórczych narażeni są na szereg powikłań potransplantacyjnych. Do najpoważniejszych z nich należy choroba przeszczep przeciwko gospodarzowi (GVHD-graft-versus-host disease), a jej występowanie stwierdza się, wg różnych autorów, w około 30–80% przypadków. Wśród często pomijanych narządów docelowych znajdują się stawy, mięśnie i powięzi.

Aim
Presentation of a case of a young patient with a chronic form of GVHD disease, who developed extensive joint changes.

Material and methods
The case of a 17-year-old patient after allogeneic bone marrow transplantation was presented, in which about 3 months after the transplantation the first symptoms of graft-versus-host disease were diagnosed. The boy developed extensive changes in the joints and fascia, allowing the patient to be qualified to Category 3 according to the NIH Consensus Criteria. The course of the diagnostic process, treatment, and rehabilitation, as well as their results at particular stages of hospitalization, are presented.

Results and conclusions
Due to the multifaceted nature of the disease, proper care and rehabilitation of patients with GvHD are not only needed for aesthetic reasons but above all to significantly restore function and improve the quality of life, especially locomotion. Early diagnosis and implementation of proper rehabilitation treatment are essential in preventing complications associated with the chronic form of the disease.

Keywords: graft-versus-host disease, allogeneic hematopoietic stem cell transplantation, joint/fascia manifestations, NIH scale

Cel
Przedstawienie przypadku młodego pacjenta z przewlekłą postacią choroby GVHD, z rozwiniętymi rozległymi zmianami stawowymi.

Materiał i metody
Przedstawiono przypadek 17-letniego pacjenta po allogenicznym przeszczepie szpiku kostnego, u którego około 3 miesięcy po transplantacji zdiagnozowano pierwsze symptomy choroby przeszczep przeciwko gospodarzowi. U chłopca rozwinęły się rozległe zmiany w obrębie stawów i powięzi, pozwalające na zakwalifikowanie pacjenta do kategorii 3 zgodnie z NIH Consensus Criteria. Przedstawiono przebieg procesu diagnostycznego, leczenia i rehabilitacji oraz ich rezultaty na poszczególnych etapach hospitalizacji.

Wyniki i wnioski
Z uwagi na wielopłaszczyznowość problemu, odpowiednie postępowanie pielęgnacyjne i rehabilitacyjne u pacjentów z GvHD nie stanowi tylko rozwiązania problemu estetycznego, lecz przede wszystkim znacznie poprawia komfort życia chorych oraz usprawnia zdolność płynnego poruszania się. Jest to bardzo ważne, ponieważ wczesna diagnoza i wdrożenie właściwego leczenia rehabilitacyjnego zapobiegają komplikacjom związanym z przewlekłą postacią choroby.

Słowa kluczowe: choroba przeszczep przeciwko gospodarzowi, allogeniczne przeszczepienie krwiotwórczych komórek macierzystych, objawy w obrębie stawów i powięzi, skala NIH

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Introduction
The first HSCT (hematopoietic stem cell transplantation) was performed at the end of the fifties of the twentieth century. Since then, the number of HSCTs has steadily increased, and each year around 20 000 to 25 000 of such procedures are performed (Toubai *et al.*, 2008; Schubert *et al.*, 2008).

Transplantation of hematopoietic stem cells is considered the treatment of choice for many types of cancer and it is also applied for primary or secondary bone marrow failure. Due to the type of donor, autologous (autoHSCT), allogeneic (alloHSCT) transplants and transplantations from syngeneic donors in the case of identical twins are available (Krzakowski *et al.*, 2013). Patients who undergo successful allogeneic hematopoietic cell transplantation are exposed to numerous post-transplantation complications (Schubert *et al.*, 2008). The most severe complication is graft-versus-host disease (GVHD) (Ferrara *et al.*, 2006; Schubert *et al.*, 2008), which is diagnosed, according to various authors, in between 30–80% of cases (Schubert *et al.*, 2008; Lee *et al.*, 2008; Hymes *et al.*, 2011). GVHD is one of the most common causes of mortality following bone marrow transplantation (Hymes *et al.*, 2011). It is caused by the donor's T lymphocyte exerting a direct cytotoxic effect on the host tissues.

The disease may develop directly after hematopoietic stem cell transplantation (acute GVHD) or even more than 100 days after the procedure (chronic GVHD) (Lee *et al.*, 2008; Hymes *et al.*, 2011).

GVHD is characterized by a diversity of symptoms. The main tissues targeted are the skin, mucous membranes of the mouth and digestive tract, eyes, lungs, genitourinary organs, liver, hematopoietic and immune systems and serous membranes (Zaucha *et al.*, 2007). Among the often-overlooked tissues are joints, muscles, and fascia. These changes predominantly affect the elbow, wrist and interphalangeal joints, which manifest themselves as stiffness, erythema, restricted range of motion, arthralgia and less-often arthritis or synovitis (Vukić *et al.*, 2016). However, edema is often the first finding on physical exam of fascial involvement in GVHD (Filipovich *et al.*, 2005).

This article presents a case of a child with overlap syndrome. It's characterized by the co-occurrence of symptoms of both acute and chronic GVHD with extensive joint involvement (Toubai *et al.*, 2008). This complication is a significant challenge for doctors of many specialties, including orthopaedists. The courses of the diagnostic process, treatment, and rehabilitation, as well as their results at particular stages of hospitalization, are presented in this article.

Aim

Presentation of a case of a young patient with a chronic form of GVHD disease, who developed extensive joint changes.

Material and method

In 2001, a 1.5-year-old male was admitted to the Pediatric Clinic of the Institute of Mother's Health in Lodz due to multiple undiagnosed symptoms. From the interview conducted with the boy's parents, it is known that the first symptoms-mycosis of the digestive system, recurrent respiratory infections, pneumonia, and bronchitis, which did not respond to standard antibiotic therapy ordered by his family doctor – appeared in infancy. Additionally, there was slight weight loss due to chronic diarrhea. During the hospitalization, multiple immune system laboratory tests were conducted. A reduction in the levels of IgG and IgA concentrations was discovered; however, the IgM concentration was at the upper limit of normal. Initially, hyper-IgM syndrome was diagnosed, and the patient was directed to the Department of Immunology of the Children's Health Center in Warsaw for extended diagnosis and possible treatment. However, due to the immunoglobulin deficiency and severe clinical course of the disease, the patient was given intravenous gammaglobulin (Endobulin 15.0 g).

In 2002, the diagnosis of primary immunodeficiency associated with increased IgM (hyper-IgM) syndrome, coupled to the X chromosome, was confirmed. The most common form of inheritance of Hyper-IgM syndrome inherited in the autosomal recessive form conjugated to the X chromosome

(Żeromski 2008). The genetic basis is the mutation of the gene encoding the ligand for CD40, i.e., CD154 (Gołąb *et al.*, 2017). CD154, binding to the CD40 on B-lymphocytes, transmits the signal necessary to class switch IgM to IgG, IgA or IgE. Lack of this receptor results in B-cell depletion at the IgM synthesis stage and the inability to switch classes (Gołąb *et al.*, 2017).

Between 2002 and 2005, the patient was under the care of his local medical center, where he received 5 g Endobulin transfusions and steroids every 4 weeks.

In May 2005, he was admitted to the Immunology Clinic at the Children's Health Center in Warsaw for a check-up and immunoglobulin transfusion. During this stay at the hospital intra- and extra-hepatic bile duct dilation on ultrasound and hepatomegaly were diagnosed. In endoscopic retrograde cholangiopancreatography (ERCP), features of primary sclerosing cholangitis were noted.

The boy was qualified for bone marrow transplantation from an unrelated donor because of the lack of HLA compatibility with both his parents and siblings. The procedure was carried out in April 2007 at the Lower Silesian Cell Transplant Center in Wroclaw.

About 3 months after the HSCT, the patient developed the first symptoms of a chronic, sclerodermic form of cGVHD (chronic graft-versus-host disease). The changes mainly affected the skin, oral mucosa, liver, and joints.

Pathognomonic skin lesions, especially those around the joints, and dystrophy of the nails were documented (Figures 1 and 2).

Figure 1. Contractures of interphalangeal joints.

Diffuse erythema, blisters, erosions, discolorations and scleroderma-like lesions were found on the skin. Microscopic examination of the skin of the forearm and elbow showed hyperkeratosis and acanthus of the epidermis with visible foci of calcifications in the dermis, which confirmed the exacerbation of chronic GVHD. These changes limited the mobility in the elbow joints to about 75 degrees. Within the wrist joints, there was a bilateral reduction in the ability to extend flexor tendons, which was confirmed by his inability to perform the "Buddha prayer" posture (Inamoto *et al.*, 2014). As the contractures progressed within all of the joints and the pain associated with it became more progressive, the boy was forced to use a wheelchair for mobility.

With the above symptoms, the patient was qualified into category 3 according to the NIH (National Institutes of Health) Consensus Criteria. The scale takes into account three components: composite score for tightness, ROM (range of motion), and activities of daily living (ADL) (Table 1) (Filipovich *et al.*, 2005).

Table 1. NIH joint/fascia scale for cGVHD.

0	No symptoms
1	Mild tightness of arms or legs, normal or mild decreased ROM AND not a ecting ADL
2	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL
3	Contracture WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self-etc.)

Figure 2. Stiffness of elbow joint secondary to sclerosis.

Additionally, the liver was diagnosed with vanishing bile ducts syndrome. Its constant deterioration of the organ led to a liver transplantation taken from the deceased donor (March 7, 2008, Department of Pediatric Surgery and Organ Transplantation CMHI) and subsequent immunosuppressive treatment.

A month later, a control biopsy of a transplanted liver revealed healthy parenchyma structure, no fibrosis, inflammatory changes or features of acute rejection.

The patient was transferred to the Gastroenterology Clinic at the Children's Health Center in Warsaw for further treatment followed by transplant team of Gastroenterology Clinic CMHI. The boy was also under the care of a psychologist due to poor mental health and reluctance to cooperate in further treatment. Currently, he rarely attends planned follow-up check-ups.

Discussion

The presented case demonstrates the importance of a broad interdisciplinary cooperation between specialists in various fields of medicine.

Symptoms presented by the patient are not limited to one specific disease and a differential diagnosis including autoimmune, dermatological and gastroenterological disorders should be considered. Such symptoms should allow the diagnostician to also suspect lupus erythematous, systemic sclerosis, rheumatoid arthritis or Sjögren's syndrome (Grkovic *et al.*, 2012).

While the range of symptoms during cGVHD is well documented, the knowledge of clinicians on the correlation between changes in the musculoskeletal system and the probability of diagnosing graft versus host disease is still relatively low. According to Kozak, pathognomonic symptoms, which are sufficient to diagnose cGVHD, include fasciitis, stiffness of the joints or secondary contracture of scleroderma (Kozak and Górska 2010).

A study conducted by Vukić *et al.*, at the University Hospital Zagreb Center, showed that out of the 29 patients with cGVHD, 12 of them (41.3%) developed join and facial lesions. The involvement of joints was more prevalent in the upper limbs, most notably in the interphalangeal, wrist, and elbow (31%). It was documented that these patients ROM was reduced by as much as 66.7% (Vukić *et al.*, 2016).

Moreover, multiple studies have presented a strong correlation between joint and skin symptoms during the course of graft-versus-host disease (Martires *et al.*, 2011; Grkovic *et al.*, 2012). According to Vukić joint changes appeared in 83.3% of subjects with coexisting erythematous lesions, superficial or deep skin sclerosis (Vukić *et al.*, 2016).

Although there is no clear consensus, it is also worth noting the possible factors influencing the development of myofascial changes in the course of cGVHD. The Inamoto *et al.*, (2014) study suggests that joint and fascia manifestations were associated with longer duration from transplantation (over a year), prevalent GVHD cases and the use of high-dose total-body irradiation conditioning. However, Vukić *et al.*, (2016) found no significant association between these parameters and joint/fascia manifestations in cGVHD.

Finally, immunosuppressive treatment and its potential adverse effects on the osteoarticular system in patients after allotransplantation should also be considered. Although this aspect was not included in the presented studies, a review of recent scientific publications demonstrated the presence of joint necrosis, loss of bone mineral density or osteonecrosis among young patients undergoing immunosuppression. High-dose corticosteroids, which are usually a first-line therapy, can also be destructive and put patients at risk of developing of myopathy. This complication appears to affect at least 40% of patients who develop GVHD after HSCT (Smith *et al.*, 2017).

Rehabilitation is a crucial element during the course of GVHD, yet not well understood

or documented. Physical therapy, occupational therapy, and assistive devices should be considered especially for those patients with poor locomotion (Smith *et al.*, 2017). Limited data suggest that only splinting and stretching may improve the range of motion of patients with fascial cGVHD, while surgical interventions may even worsen fascia restrictions (Beredjiklian *et al.*, 1998).

Smith and Asher provide data suggesting muscle atrophy may be reduced in patients thought resistance exercise training, especially when done before or during steroid use (Lapier 1997). These studies underline the critical role that rehabilitation plays in the improvement of the quality of life of patients with GVHD complications and should be personalized to the patient's needs, to exert an optimal effect.

Conclusions

Graft-versus-host disease is considered the most common complication after allogeneic bone marrow transplantation. Due to the multifaceted nature of the disease, proper care and rehabilitation in patients with GVHD are not only needed for aesthetic reasons but above all to significantly restore function and improve the quality of life, especially locomotion. Early diagnosis and implementation of proper systemic treatment are essential to prevent complications associated with the chronic form of the disease.

It is also worth emphasizing the importance of proper cooperation of the patient and his parents during the treatment. Through education, the patient's understanding of the disease, the need of taking their medication and importance of regular checkups, significantly increases the chances of successful treatment.

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