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Drug-induced hypersensitivity syndrome: a literature review and a case report

Abstract

Drug-induced hypersensitivity syndrome (DIHS) is characterised by fever, rash and an involvement of the internal organs, mainly the liver, myocardium, kidneys or lungs, which may develop within 1–8 weeks after exposure to the offending drug. An increase in body temperature is generally the first sign, followed by erythematous skin eruptions, although the severity of skin changes does not parallel the severity of internal organ involvement. It is believed that anti-epileptic drugs (particularly carbamazepine), antibiotics and allopurinol are the commonest causes of DIHS. The pathomechanism of the syndrome is unclear, although defects in the detoxification of reactive drug metabolites and genetic predisposition have been implicated. The diagnosis of DIHS is based on the characteristic manifestations triggered by the drug and may be supported by eosinophilia, elevated markers of inflammation and abnormal organ function tests, such as liver function tests. Management involves immediate discontinuation of all suspected drugs and initiation of glucocorticosteroids. We report the case of a 72 year-old female who developed manifestations of DIHS after about four weeks of treatment with an anti-epileptic drug (carbamazepine) for sensory axonal polyneuropathy. Discontinuation of the offending drug and initiation of systemic glucocorticosteroids resulted in resolution of the clinical manifestations.

Key words: drug-induced hypersensitivity syndrome, carbamazepine, hepatitis

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Introduction

Drug-induced hypersensitivity syndrome (DIHS) is characterised by a skin rash, elevated temperature and an involvement of the internal organs (mainly the liver and kidneys) with a proved causal relationship between the drug and the manifestations.

Bocquet et al. [cited in: 1–3] extended the definition and introduced the term DRESS (drug rash with eosinophilia and systemic symptoms). The most commonly implicated drugs include anti-epileptic drugs (mainly carbamazepine, phenytoin, phenobarbital, lamotrigine), antibiotics (minocycline, β -lactams, sulfonamides), antiviral agents (abacavir, nevirapine), dapsone, sulfasalazine, and allopurinol [3–6].

Callot et al. [cited in: 7] observed DIHS following treatment with diltiazem and mexiletine. The pathomechanism of the syndrome is unclear, although it is arbitrarily assumed that the drug-induced manifestations are associated with cytochrome P450 dysfunction and the presence of biologically reactive drug metabolites in the circulation [5, 7]. These metabolites may activate macrophages, eosinophils and T cells, which results in the release of cytokines, mainly IL-5 [3, 4]. Recent bibliographical data also suggests a possible reactivation of certain viruses in the course of DIHS, such as herpesvirus (HHV-6, HHV-7), Epstein-Barr virus (EBV) or cytomegalovirus (CMV), which is associated with the replication of viral DNA by the stimulated immunocompetent cells [2–5, 8]. The first manifestations of DIHS usually develop wi-

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thin about 1–8 weeks after initiation of the above mentioned drugs [2, 3, 6, 9]. The increase of body temperature and the development of erythematous skin rash involving various areas of the body, most commonly the face, upper trunk and extremities, sometimes accompanied by facial oedema and changes in the lips and oral mucosa, and an involvement of internal organs, such as the liver, kidneys or, less frequently, the lungs and heart, are observed. Cases of DIHS with peripheral lymphadenopathy and with an involvement of the thyroid gland and the central nervous system have been reported [2, 4, 6, 10]. Differential diagnosis should include bacterial and viral infections, lymphoproliferative disorders, autoimmune diseases, serum sickness and adult-onset Still's disease [3]. Laboratory tests in patients with DIHS reveal elevated markers of inflammation (WBC, CRP, ESR), eosinophilia in the peripheral blood, elevated ALT and AST and/or elevated serum creatinine [3, 4, 9]. Histopathology of a skin biopsy collected from the affected areas is usually nonspecific. It most commonly reveals a predominantly lymphocytic perivascular inflammatory infiltrate in the dermis with or without eosinophils [2, 11]. The diagnosis of DIHS may be based on the criteria proposed by Bocquet et al. in 1996 and modified by Roujeau et al. in 2005 [cited in: 2, 3], which include: fever, drug-induced skin eruption, eosinophilia and/or presence of atypical lymphocytes in peripheral blood. The above changes are accompanied by clinical criteria, such as: hepatitis with elevated aminotransferases, renal dysfunction with elevated serum creatinine, peripheral lymphadenopathy, interstitial pneumonia and myocarditis proved to be drug-induced. The diagnosis requires the presence of at least three of the above criteria [3, 11]. In addition to the discontinuation of the offending drugs, the management of DIHS involves administration of moderate doses of systemic glucocorticosteroids, which are particularly recommended in cases of extensive involvement of the internal organs [3, 11]. If the patient fails to improve despite systemic glucocorticosteroids, plasmapheresis or administration of intravenous immunoglobulin (IVIG) should be considered. The efficacy of *N*-acetylcysteine is also being discussed. Being the precursor of glutathione, which is involved in detoxification processes, it might speed up the elimination of the offending drugs, mainly anti-epileptic agents [2, 7].

Case presentation

A 72 year-old female without medical co-morbidities was admitted on 4 January 2010 to the

Department of Internal Diseases, Geriatrics and Allergy, Medical University of Wrocław, Poland (hospital case number 00456/10) for acute disseminated maculopapular rash accompanied by a fever of 38°C and malaise.

According to the history provided by the patient, in December 2009 (four weeks after receiving Vaxigrip®, an inactivated polyvalent influenza vaccine) the patient developed numbness in her feet, lower legs, arms and forearms, for which she was hospitalized at the Department of Neurology, Military Teaching Hospital in Wrocław from 11 to 18 December. Based on the diagnostic investigations performed at that time, a diagnosis of sensory axonal neuropathy was made, and the patient was started on Amizepin (carbamazepine) 200 mg PO tid, which she continued to take until the hospitalization at our Department. On admission, the patient was in a moderate condition. Blood counts revealed normal WBC and PLT counts and no eosinophilia (WBC $4.54 \times 10^3/\mu\text{L}$, PLT $213 \times 10^3/\mu\text{L}$, eosinophils $0.21 \times 10^3/\mu\text{L}$), blood coagulation parameters were normal (TT 19.1 s, INR 1.05). CPR and ESR were elevated (55.03 mg/L and 54 mm at 1 hour, respectively). Biochemistry revealed signs of hepatocellular injury manifested by progressive elevation of AST (up to 233 U/L), ALT (up to 512 U/L), GGT (up to 969 U/L) and ALP (up to 306 U/L), without signs of hepatomegaly, changes in liver sonographic structure or deposits in the gallbladder on abdominal ultrasound. Renal parameters were normal (urea 34 mg/dL, creatinine 0.89 mg/dL, eGFR 66 ml/min). Urinalysis revealed microscopic haematuria. An assessment of the complement system revealed reduced C3 and C4 (0.72 g/L and 0.08 g/L, respectively). Total IgE levels were elevated (94.3 IU/mL). Investigations for connective tissue diseases and autoimmune diseases (ANA, p-ANCA, c-ANCA, anticardiolipin antibodies) were all negative and rheumatoid factor was undetectable. Thyroid function was normal and anti-TG and anti-TPO were not elevated. Investigations for hepatitis B and C were negative. Cancer markers were negative. The biopsies collected from the affected skin areas localised on the anterior aspect of the upper trunk were examined by a pathologist (Report 34982/2010). They revealed chronic inflammatory infiltrates in the dermis around vessels and skin appendages consisting predominantly of small lymphocytes, plasma cells, neutrophils and a few melanophages and isolated eosinophils (Fig. 1). Following initiation of systemic glucocorticosteroids (methylprednisolone i.v., followed by PO) the fever subsided and we observed a gradual resolution of the skin changes, normalization of the in-

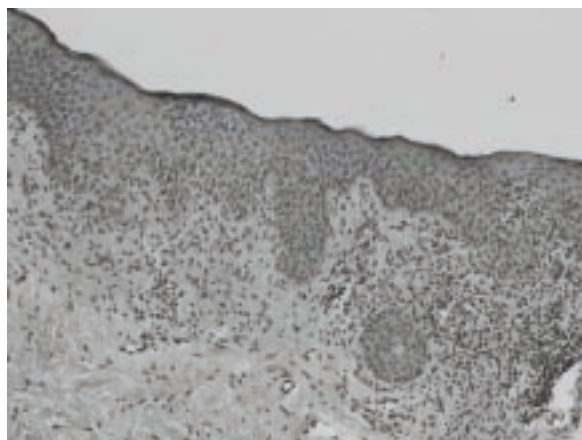


Figure 1. Histopathological examination of skin biopsy (No. 34982/2010) — description in the text

flammation markers, liver enzymes and of microscopic haematuria on a follow-up urinalysis. The patient's clinical condition improved, which allowed us to discharge her with a recommendation to undergo further management in the outpatient setting.

Discussion

According to the World Health Organisation (WHO) definition, an adverse drug reaction (ADR) is any harmful and unintended effect that occurs during the use of recommended doses of a drug for prophylactic, diagnostic or therapeutic purposes, irrespective of the route of administration. ADRs may be a significant problem and their commonest form is maculopapular rash. It is estimated that ADRs may affect about 1.5–7.0% of the general population and about 10–20% of hospitalized patients [12]. The clinical manifestations of the skin reactions correspond to various types of allergic reactions, with the skin being particularly predisposed towards exhibiting the signs and symptoms of hypersensitivity due to the presence of antigen-presenting cells, lymphocytes, keratinocytes and enzymes that metabolise low-molecular-weight molecules. The skin is also known to be a site of extrahepatic drug metabolism and may therefore convert carbamazepine into a derivative of high affinity for proteins, which may partially explain why the drug causes DIHS with a predominantly cutaneous presentation [13]. DIHS was first described in 1950 by Chaiken et al. [cited in: 2, 3] and its prevalence is estimated at between 1 per 1,000 and 1 per 10,000. While most patients quickly recover, the prognosis is worse in elderly or immunocompromised patients. No association between the prevalence of DIHS and age has been demonstrated, nor any seasonality observed. DIHS has

also been reported in children, in whom establishing the correct diagnosis may be difficult, as based on the clinical presentation (fever, maculopapular rash, hepatomegaly) a diagnosis of viral infection, mainly infectious mononucleosis, is initially made [2, 3, 14].

Our clinical case meets the diagnostic criteria of DIHS established on the basis of the available medical literature. Elevated temperature, maculopapular rash, hepatocellular injury and elevated markers of inflammation, all typical of DIHS, were present in our patient. Also the onset of the symptoms (about four weeks following exposure to the offending carbamazepine) fell within the 1–8 weeks timeframe and seems to confirm the causal relationship between exposure to the drug, which is most commonly implicated in DIHS, and the onset of symptoms. It should be noted that the direct reason for initiating carbamazepine was the diagnosis of sensory axonal polyneuropathy, which developed within 4–5 weeks after administration of an inactivated trivalent seasonal influenza vaccine (Vaxigrip®). These neurological manifestations may be considered an adverse post-vaccination reaction, and similar cases have been reported [15, 16].

We must point out here to the difficulties in differentiating manifestations of DIHS from those of serum sickness, which may also develop following vaccination [17, 18]. The timing of symptoms and the results of the histopathological examination of the skin biopsies allowed us to establish the diagnosis of DIHS. Our patient was not using any other medications during that period (i.e. between December 2009 and January 2010). Because of the fever just prior to the hospitalization, the patient used paracetamol 500 mg PO, which is not listed as a possible cause of DIHS, but could have been an additional triggering factor.

The investigations carried out as part of differential diagnosis in our patient ruled out other diseases in which skin changes may be the first manifestation, such as haemorrhagic diatheses, systemic connective tissue diseases, rheumatoid arthritis, hepatitis B and C, autoimmune thyroiditis, and cancer. Also the skin biopsy results, consistent with case reports describing patients with DIHS available in the literature, additionally supported our diagnosis. It should be emphasized that the elimination of the causative factor (Amizepin) and initiation of the standard recommended treatment (systemic glucocorticosteroids at tapered doses and, supportively, antihistamines) resulted in an improvement of the patient's clinical condition and resolution of both cutaneous and systemic manifestations.

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