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A patient infected with SARS-Cov-2 presents with DIHS syndrome induced by olanzapine: diagnostic difficulties

Review

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Abstract

Drug-induced hypersensitivity syndrome (DIHS) is a potentially life-threatening reaction. The pathology of DIHS has been connected with adverse reactions to drugs; however, it has been observed that viruses and other infectious factors may induce similar responses in the body. COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently become a major challenge for worldwide healthcare. The dermatological symptoms occur in approximately 5.95% of COVID-19 patients, however, they are not exclusively a manifestation of SARS-CoV-2 infection.

Certain skin-related symptoms might result from therapeutic drug administration, personal protective equipment, or sanitizers used by medical personnel. The complex pathomechanism of those symptoms leads to multiple diagnostic difficulties. This article describes a case of a 40-year-old man who was admitted to the intensive care unit (ICU) due to heavy respiratory failure in the course of SARS-CoV-2 infection. The patient has been treated with olanzapine for anxiety disorder for approximately 4 years. On the seventh day of treatment, the patient presented with a maculopapular rash, fever, and swollen upper lip. Because of these presented symptoms, the patient has been diagnosed with drug-induced hypersensitivity syndrome (DIHS). The results of blood analysis showed elevated levels of acute phase markers, liver and kidney damage markers, which are present both during COVID-19 and DIHS. Furthermore, the patient presented with peripheral eosinophilia, which is a distinctive feature of DIHS. In the course of COVID-19, the laboratory-measured levels of eosinophilic granulocytes declined to 0. Therefore, in the active phase of SARS-CoV-2 infection, the eosinophilia connected with DIHS was difficult to assess.In this paper, we compare and contrast the clinical and laboratory symptoms of COVID-19 and DIHS syndrome, describe patient's case and explain the diagnostics difficulties resulting from the concomitance of those disease entities.

Keywords

drug-induced hypersensitivity syndrome • drug reaction with eosinophilia and systemic symptoms COVID-19 • olanzapine

1. Introduction

Drug-induced hypersensitivity is known to influence various organs, however, the symptoms are primarily associated with and observed on the skin. Mortality, dependent on various factors, is observed in 10% of patients. Drug reaction with eosinophilia and systemic symptoms (DRESS) is described as increased activity of the immune system combined with eosinophilia, fine-grained rash, and systemic symptoms caused by mainly antiepileptic drug–induced hypersensitivity [1,2]. However, similar symptoms have been observed after the distribution of other kinds of drugs, therefore, to unify the terminology, drug-induced hypersensitivity syndrome (DIHS) was proposed.

Ever since its first outbreak in 2019, SARS-CoV-2 remains a challenge for worldwide healthcare. Cutaneous manifestations of COVID-19 occur in 5.95% of infected patients [3].

1.1. Drug-induced hypersensitivity

The frequency of DIHS is estimated between 1:1000 and 1:10000 in patients undergoing pharmacotherapy [4]. The age median upon diagnosis is 50–55 years and approximately 7% of cases are found among patients under 20 years of age [5]. Organ manifestations with systemic reactions are rarely diagnosed due to the diversity of clinical symptoms. They are most often connected with the liver, kidneys, lungs, and skeletal muscles, but rarely the spleen, pancreas, or digestive system [6,7,8]. The mortality rate is 10–15% and it is visibly correlated with the status of renal and liver involvement [9].

The first case of DRESS was described by Chaiken et al.who observed characteristic DRESS symptoms in a patient given Dilantin for antiepileptic treatment [10]. It has been shown that DIHS and DRESS are connected with specific variants of human leukocyte antigens (HLAs), the most prominent ones being HLA-B*1502, HLA-B*1508, HLA-B*5701, and HLA-B*5801, HLA-B*3101 [11,12,13,14]. Therefore, the presence of specific HLAs correlates with susceptibility to DIHS depending on the patient's ethnic origin [15]. In recent findings, there has been a slight increase in the diagnosis of DIHS in women [16]. Notably,

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it is believed that previous rheumatoid diseases may affect the frequency of DIHS occurrence.

Researchers have shown a strong correlation between drug intake and symptom occurrence in DIHS [17,18,19]. Drugs that are most often responsible for DIHS are antiepileptic drugs containing aromatic compounds (carbamazepine, lamotrigine, phenytoin), mood stabilizers (carbamazepine), and tricyclic antidepressants [12,20,21,22,23]. Cases of DIHS caused by sulfonamides, sulfones, or antibiotics are also present in the literature [19,24,25].

Despite rising interest among researchers, the pathomechanism of DIHS is not entirely defined. It is unknown whether infection factors catalyze allergy-related cytokines or if there is a cross-reaction induced by the immune cells responding to the distributed drug. From a molecular perspective, the probable origin of drug-induced reactions is the dysfunction of P450 cytochrome, namely, the polymorphism of its coding gene: *CYP1A2* [26]. Combined with the concentration of active metabolite particles in the serum, both of those factors influence the biotransformation of the drug.

In recent years, viral influence in DIHS has been highlighted [27]. Herpesviruses (HHV6, HHV7), herpes simplex, cytomegaloviruses (CMV), and Epstein-Barr viruses (EBV) are considered important for DIHS [28]. The viral replication causing an overall immune response prolongs the occurrence of DIHS symptoms and the recovery period, and increases the chance of a patient's relapse. A hypothesis suggests that viral infection triggers the activity of T lymphocytes and therefore increases their chances to cross-react with a drug. Additionally, this results in the decrease of B lymphocytes, selective IgA deficiency, and low concentration of serum IgG, which weakens the inhibition of viral infection. Therefore, DIHS results from multiple interactions relevant to drug exposure, viral infections, and genetic predispositions of the patient [29]. The histopathological analysis of skin biopsy oftentimes shows inflammatory infiltrate which consists mainly of lymphocytes and eosinophils in the vascular system of the dermis [30]. Due to the abundance of symptoms, DIHS is often described as "the great mimicker" of other systemic diseases, which influences precise diagnostics [31].

The diagnosis of DIHS is based on the RegiSCAR scale which includes criteria such as eosinophilia, lymphocyte level deviations and other laboratory abnormalities, skin rash type and extent, as well as lymph node enlargement and at least one organ involvement [32]. Organ involvements include mostly hepatitis suggested by elevated levels of alanine aminotransferases (ALT) and aspartate aminotransferase (ASPAT), whereas increased levels of creatinine indicate kidney injury or muscle inflammation, including both skeletal and cardiac muscles [27,33].

The scale established by Shiohara et al. involves HHV-6 reactivation and prolonged clinical symptoms of DIHS after discontinuation of the pharmacotherapy along leukocytosis and leukocyte abnormalities, lymphadenopathy, and prolonged clinical symptoms after discontinuation of the potentially causative drug [2]. In recent years, the Japanese consensus group proposed a new prognostic scale for DIHS/DRESS based on the intensity of fixed parameters (age, duration of causative drug exposure, onset) and variable parameters including skin, liver, and renal involvement, percentage of body surface area with erosions and rashes, as well as the levels of CRP [34].

Currently, diagnosis of DIHS is based upon the presence of 7 criteria mentioned above or 5 criteria in terms of atypical DIHS. The therapy of choice is to discontinue the administration of the drug which is a potential cause of hypersensitivity. If the drug can't be specified, a positive lymphocyte transformation test may confirm the drug that is the cause of DIHS [35]. In addition, the use of systemic glucocorticoid therapy is recommended. Moderate doses influence symptoms of late hypersensitivity, as well as lymphocyte activation [36]. In case of arising clinical symptoms, parenteral plasmapheresis or immunoglobulin distribution is advised. Moreover, to accelerate drug elimination from the system, N-acetylcysteine can be administered [37]. The complementary treatment includes antihistamine and antipyretic drugs, water and electrolyte supply, or topical skin treatment.

1.2. SARS-COV-2

SARS-CoV-2 is a member of the *Coronaviridae* family. It is an enveloped, positive-stranded RNA virus of zoonotic origin [38,39]. It was first identified in Wuhan, China in November 2019 where it was responsible for a novel type of viral pneumonia that has been labeled as COVID-19 [38,14]. Due to its high transmission and infectiousness, SARS-CoV-2 has quickly spread all over the world and became a major challenge for worldwide healthcare in the twenty-first century [38].

The molecular mechanism of SARS-CoV activity begins when the viral S protein binds with the angiotensin-converting enzyme 2 (ACE2) receptor, which is mainly expressed in the epithelial cells [38,40,41]. Most often, SARS-CoV-2 binds with the ciliated cells of nasal epithelium, where it replicates and migrates throughout the rest of the respiratory tract, with particular affinity for bronchial epithelia and type II alveolar cells [38,42]. Except from the respiratory tract, notable amounts of ACE2 receptors can be found in the myocardium, gastrointestinal tract, kidneys, and thyroid, whereSARS-CoV-2 can also reside [43,44,45]. SARS-CoV-2 infection causes systemic immune response, such as cytokine storm and acute respiratory distress syndrome leading to respiratory failure [46,47].

In the course of COVID-19, the number of cytotoxic T-cells and natural killer cells of infected patients are significantly lower compared with healthy patients [48,14]. The activity of cytotoxic cells is necessary for eliminating viral infection [38]. The lack of proper immunological response might result from various factors such as age, disease progression, coexisting health conditions, or

concomitant therapies that impair the response of the immune system [49]. Notably, SARS-CoV-2 significantly lowers the levels of eosinophils of infected individuals, sometimes to the point of making eosinophils undetectable [50,51]. What is more, eosinopenia was reported to be lower for patients with COVID-19 than in patients with other types of pneumonia [52]. General symptoms of COVID-19 include fever, cough, shortness of breath, and fatigue, which occur in the vast majority of patients infected with SARS-CoV-2 [53,38,54].

Cutaneous manifestations of COVID-19 occur in 5.95% of infected patients. Maculopapular rash has been reported most often, usually in patients with intermediate severity of the disease [55]. Other common skin lesions were acral areas of erythema, vesicular eruptions, urticarial lesions, and necrosis. Patients reported mostly pruritus, stinging, and pain [3]. Furthermore, multiple organ failure has been observed in various cases of COVID-19, particularly in elderly patients as well as individuals presenting other risk factors, such as hypertension, diabetes, and immune deficiencies [38,14,56].

Therapy for SARS-CoV-2 infection has been the biggest challenge for worldwide healthcare for over the past two years. Notably, drugs that are currently used in COVID-19 pharmacotherapy, such as antiviral drugs such as oseltamivir or immunomodulatory agents might result in maculopapular skin lesions as well [1,57,58].

2. Case report

A 40-year-old man was admitted to ICU on November 2021 due to acute respiratory distress syndrome (ARDS) as a result of a massive, bilateral pneumonia caused by SARS-CoV-2 infection. The patient's medical history showed that four years prior, he has been diagnosed with anxiety disorder and had been treated with 5 mg of olanzapine daily ever since. The patient had no other chronic diseases. In the emergency unit, passive oxygen therapy was supplied; however, due to a lack of improvement and developing hypoxemia, the patient was submitted for mechanical ventilation with a respirator. At the ICU, the patient was put in conscious sedation and remained in logical contact. The applied sedative was dexmedetomidine, according to current ICU guidelines.

At first, antibiotic therapy was not administered.Periodic diuresis was stimulated with torasemide. The patient was fed intragastrically via a nasogastric tube.Olanzapine administration was continued according to the psychiatric recommendation, to prevent sedative withdrawal symptoms when the sedation ended. The applied treatment stabilized and gradually improved the overall state of the patient. The improvement was measured through ventilation parameters and decreasing demand for substituted oxygen.

On Day 7 of hospitalization, the patient presented with significant swelling of the upper lip, as well as maculopapular rash, mainly in the thorax area. The skin lesions were followed by increased levels of ALT and slightly increased levels of inflammatory markers, such as C-reactive protein (CRP), procalcytonin (PCT), and eosinophils alongside fever reaching 40 degrees Celsius. Microbiological tests were performed, for which the material was derived from blood, urine, and tracheal aspirate, all of which showed negative results. The vascular and urinary catheters were changed for new ones. Antihistamine was introduced into the treatment and the dosage of dexamethasone was increased. After two days, the skin lesions decreased in size. The patient's state remained stable. Due to the improvement of ventilation parameters, the patient's awakening from the induced coma was decided and therefore the administration of dexmedetomidine was reduced.

Concurrently, after psychiatric consultation, the dosage of olanzapine was increased to further decrease the symptoms of sedative withdrawal.

On Day 10 of hospitalization, the patient's state worsened and the 40 degrees Celsius fever returned. Administration of noradrenalin and enoxaparin was required to stabilize the patient's vascular system. In the blood smear assay, there was an increased level of eosinophils. Empirical antibiotic therapy was introduced. Once again, microbiological tests were performed. *Staphylococcus aureus* was cultured from the tracheal aspirate sample, while from blood, *Acinetobacter baumani* was cultured. The antibiotic administration was modified based on de-escalation therapy.

An increase in the skin lesions was observed in the form of a maculopapular confluent rash. DIHS syndrome was suspected, and during the next days of the patient's hospitalization, a section of the skin and subcutaneous tissue was biopsied for histological analysis.

Among other symptoms, the eosinophilic infiltration of the tissue found in the biopsy was the most significant. A comparison with the description of DIHS present in the corresponding research articles constituted the diagnosis of drug-induced hypersensitivity. Steroids have been implemented into the treatment to stop the symptoms of drug hypersensitivity.

The patient received 6 mg of dexamethasone daily; however, when the symptoms became more severe, the dosage was increased to 24 mg daily. The antihistamine treatment was modified by changing clemastine for rupatidine. As a result, the patient's state significantly improved.

On Day 18 day of hospitalization, the patient was fully awakened from the coma. On Day 19, mechanical ventilation ended. The patient was discharged from ICU after three weeks on December 2021 in good general condition on Day 23 and was admitted for further treatment at the neurological rehabilitation unit due to observed mild polyneuropathy. A detailed description of the patient's blood test parameters and their changes during hospitalization is shown in Table 1.

Table 1. A detailed description of patient's blood morphology throughout the treatment process and additional key symptoms observed in the process

	Days of hospitalization					
	7	9	10	11	13	14
Parameter value in PB						
Leukocytes [$10^3/\mu l$]	9.77	7.47	6.03	9.38	5.9	6.27
Neutrophils [%]	82.7	62.1	84.1	79	57.4	62.4
Eosinophils [%]	1.6	12	2	1.5	13.4	8.8
Basophils [%]	0.2	0.8	0	0.2	1	0.6
Lymphocytes [%]	12	15.3	9.1	15.4	21.5	21.5
Monocytes [%]	3.4	9.8	4.8	3.9	9.7	6.7
Erythrocytes [$10^6/\mu l$]	4	3.5	3	3.2	3.5	3.6
Hemoglobin [g/dl]	11.2	10.4	8.5	9.3	10.1	10.3
Hematocrit [%]	34.3	31.4	25.7	27.3	30.1	29.8
MCV [$10^{-15}/\mu l$]	86.4	89	85.7	84.5	87	83.5
MCH [pg/cell]	28.2	29.5	28.3	28.8	29.2	28.9
MCHC [g/dl]	32.7	33.1	33.1	34.1	33.6	34.6
RDW-CV [%]	12.9	14.9	13	13	14.1	13.8
PLT [$10^{-15}/\mu l$]	310	365	181	228	305	322
MPV [$10^{-15}/\mu l$]	11	11	12.7	12.9	10.6	10.9
AspAT [U/l]	87			64		
AlAT [U/l]	109			97		
CRP [mg/l]	89.5	8.13	73.2	131	19.1	21.4
CK [U/l]				1144		

PB – Peripherical blood
On Day 7 of hospitalisation, patient presented with an upper lip swelling and maculopapular rash. On Day 9 of hospitalisation, the rash and the swelling have decreased. On Day 10, after olanzapine administration was increased, the patient presented with a 40°C body temperature and eosinophilia visible in the blood smear. On Day 13, patient was diagnosed with bacterial infection of ***Staphylococcus aureus and Acinetobacter baumani****. The antibiotic therapy as well as antihistamine treatment were modified. Since then, patient's state was gradually improving until discharge from the ICU on Day 23.*

3. Discussion

Drug-induced acute reactions remain a challenge in clinics due to the heterogeneity of their symptoms [17,57,58]. The morphology of skin lesions that occur during DIHS do not present specific characteristics based on the administered drug. Moreover, the same drug can cause a variety of morphological changes on the skin or in the internal organs. Oftentimes, the symptoms are similar to the ones observed during viral or bacterial infections as well as systemic diseases of connective tissue [57].

According to Shiohara et al., herpes viruses are oftentimes involved in the pathomechanism of DIHS [2]. Moreover, the severity of early symptoms of DIHS has been shown to correlate with HHV-6 reactivation [59]. Similarly, EBV, HHV-7, and CMV have been shown to sequentially reactivate in DIHS, which contributes to the intensity of the symptoms and the time of their occurrence consequently [60,61]. Despite the relationship between DRESS/DIHS and viral reactivation, it is important to note that it is not present in all cases. It is due to the fact that viral antigens might not always be detectable in peripheral blood, which can happen, for example, if viral reactivation occurs in the spleen or lymphatic nodes.

Olanzapine is an atypical, antipsychotic drug classified as tienobenzodiazepin.

Its mechanism of action is based on blocking primarily dopamine (D2) and serotonin (5-HT2) receptors [62]. The metabolism and detoxification of benzodiazepines involve oxidative metabolism in cytochrome P450, encoded by the *CYP1A2* gene, which is active primarily in the liver and kidneys [63].

In drug-induced cutaneous hypersensitivity, the main cause is drug metabolism defects.

Such defects are most often related to either quantitative or qualitative oxidative enzyme deficiency [30]. For instance, one of the most often reported ones is the defects of epoxide dehydrogenase, an important factor in aromatic ring metabolism [11].

The case of this patient matches the diagnostic criteria for DRESS/DIHS based on the available literature. Considering all of the observed symptoms and laboratory parameters, according to RegiSCAR scale the patient was classified grade 8 [34].

Main diagnostic difficulties originated from the concurrent treatment of SARS-CoV-2 infection. Increased body temperature, maculopapular rash, kidney and liver damage, as well as increased levels of biochemical inflammatory markers all together present a typical picture of drug-induced hypersensitivity. Moreover, the olanzapine administration, which was increased throughout the therapeutic process, is correlated with the increased severity of

the patient's symptomsof DIHS. In the additional analysis, there was a persistent level of IgG against CMV and a lower level of IgG against EBV, which were additionally influencing DIHS.

The observed increase of CRP, kidney and renal damage as well as increased body temperature can be found both in COVID-19 and DIHS. In our case, the occurrence of rash correlated with the increase of ALT levels, namely ASPAT to 87 x 10^6 / µl (the norm is 5-38 x 10^6 / µl) and ALT to 109 µl (the norm is 5-41 x 10^6 / µl). Total bilirubin levels remained within the norm; however, we observed a temporary increase of serum creatinine level to 1.35 mg/dl (the norm is 0.7–1.2 mg/dl) and an adequate decrease of glomerular filtration rate to 65.2 ml/min/1.73 m^2 (the norm > 90 ml/min/1.73 m^2).During the first episode of rash, we also observed an increase in CRP with no signs of bacterial infection to 131 mg/l (the norm is < 5 mg/l). Additionally, the levels of pancreatic amylase temporarily increased to 205 x 10^6 /µl (the norm is 0-100 x 10^6 /µl).

Similar report was described by Cruz et al. who presented a case of a 36-year-old obese male patient treated for hypertension and anxiety disorder with carbamazepine and escitallopram, which are common mood stabilizers [64]. The patient tested positive for COVID-19 on Day 8 of hospitalization. Interestingly, this patient developed maculopapular rash on Day 12 of hospitalization, which deteriorated over time along with other symptoms suggesting DIHS, such as liver involvement. Along with the progression of skin-related symptoms the patient presented with increasing eosinophilia (1.132/µl on Day 8 and 3.198/µl on Day 14). The condition of the patient's skin began to improve only when carbamazepine was discontinued on Day 43 of hospitalization [38]. Based on presented symptoms the patient was classified grade 6 on the RegiSCAR scale [34].

Ramirez et al. described a series of cases of COVID-19 patients with simultaneous DIHS occurrence, likely caused by the administration of hydroxychlorquine and antibiotics [65]. Notably, one of the patients was a 56-year-old female patient with history of hypertension, diabetes, depression, and anxiety disorder who tested positive for COVID-19 upon admission to the hospital. The patient was treated long-term with fluvoxamine and promazine and received antibiotics and antiviral drugs during her hospitalization. The patient developed intense eosinophiia (5300/µl) on Day 14 of hospitalization followed by extensive maculopapular rash on Day 30 of hospitalization. Additionally, liver and kidney involvement was reported. Based on presented symptoms the patient was classified grade 6 on the RegiSCAR scale [34].

Herman et al. mentioned a case of a 50-year-old male patient who was admitted to ICU due to ARDS resulting from an ongoing SARS-Cov-2 infection [58]. The patient had no history of previous psychiatric treatment, however, he received azithromycin and hydroxychloroquine prior to his admission. Notably, the patient received clonidine and norepinephrine at admission. On Day 9 of hospitalization, the patient developed maculopapular rash over a large area of his body. Laboratory analyses showed elevated levels of CRP and D-dimers as well as absolute eosinophilia (950/µL). Based on altered levels of ALT (59 x 10^6 / µl), creatinine, and other markers, kidney and liver involvement were observed as well [57]. Presented symptoms were classified as DRESS and the patient obtained grade 7 on the RegiSCAR scale. According to the DRESS prognostic scale proposed by Shiohara and Mizukawa, the patient's prognosis was deemed severe [23,34].

4. Conclusions

In the described case, both olanzapine treatment and concurrent SARS-CoV-2 infection were mutually respoinsible for the occurrence of DIHS. On one hand, eosinopenia is likely to occur during COVID-19. On the other hand, DRESS/DIHS is characterized by peripheral eosinophilia, which was evident among other case reports that we analyzed. In our patient, the levels of eosinophils rose and decreased alternately in the course of active COVID-19 prior to DIHS, which makes our case quite atypical. Therefore, during active SARS-Cov-2 infection, the eosinophilia characteristic of DRESS/DIHS might be much more difficult to diagnose than without the infection. From a clinical perspective, it is important to properly assess the eosinophile levels of the patient, due to the fact that both of the described diseases contrarily influence eosinophils.

Abbreviations

ACE2 - Angiotensin-converting enzyme 2
ALT – Alanine transmainases
ARDS – Acute respiratory distress syndrome
ASPAT - Aspartate aminotransferase
CMV - Cytomegalovirus
CRP - C-reactive protein
D2 - Dopamine and serotonin
DIHS - Drug-induced hypersensivity syndrome
DRESS – Drug reaction with eosinophilia and systemic symptoms
EBV - Epstein-Barr virus
HLAs – Human leukocyte antigens
HHV6, HHV7 - Herpesviruses 6 and 7
PCT - Procalcytonin
SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2
5-HT2 – Serotonin receptor

Authors' contribution

M.S and M.C were responsible for providing clinical informations; M. C and M.P were responsible for the acquisition of literature for the manuscript; M.P wrote the original draft of the manuscript with input from all authors. All authors have read and agreed to the published version of the manuscript.

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Conflict of interests

The authors have no potential conflicts of interest to declare.

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