CASE REPORT

Positive Herpesvirus IgG Antibodies in Lung Cancer Patients Finally Proved as Drug-induced Pemphigus

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SUMMARY

Background: Herpesvirus IgG antibody positivity can be a lifelong burden of disease replication and reinfection or recent viruses can be reactivated and play an important role in the diagnosis and monitoring of herpesvirus [1]. However, sometimes serum IgG antibody positivity is of limited help in determining the onset of disease. We reported a case of herpesvirus IgG antibody positive in a patient with lung cancer who was initially misdiagnosed as herpes simplex and later confirmed drug-induced pemphigus (DIP) by histological and immunofluorescence studies.

Methods: Appropriate laboratory tests, enzyme-linked immunosorbent assay (ELISA), immunofluorescence and histological tests were performed for diagnosis.

Results: In lung cancer patients who were positive for herpesvirus IgG antibodies, were initially misdiagnosed as herpes simplex and eventually confirmed by histological and immunofluorescence examinations as DIP.

Conclusions: Positive herpesvirus IgG antibody is not a specific manifestation of herpesvirus infection. For patients with unexplained skin blisters, we should improve histological examinations as soon as possible to clarify the type of lesion.


KEYWORDS

herpesvirus IgG antibodies, herpes simplex, drug-induced pemphigus, histology, immunofluorescence

CASE REPORT

Pemphigus is a chronic, life-threatening autoimmune disease characterized by blistering of the skin and mucous membranes that produces autoantibodies against intercellular adhesions. Among them, drugs are considered to be the main predisposing factors [2]. DIP refers to a specific type in which drugs play a major role in the pathogenesis [3]. The disease typically has an incubation period of days or even months, with early nonspecific cutaneous manifestations such as morbilliformis, erythema annoids, urticaria-like rashes, and general drug eruptions, and later vesicular lesions that are difficult to distinguish from herpesvirus [3]. Direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) are often used for diagnosis [4], and the positive
rates of the disease are 75% - 90%, 50% - 70%, respectively, increasing the misdiagnosis rate. In this article, a patient with herpesvirus IgG antibody positive for DIP was initially misdiagnosed as herpes simplex in a lung cancer patient and the clinical data were analyzed to improve the understanding of the disease.

The patient, a 53-year-old man, presented to our hospital in March 2023 with the main complaint of "diagnosed small cell lung cancer with fever for 2 days in 2 months". Two months ago, the patient was diagnosed with small cell lung cancer in our hospital due to "cough and sputum for more than 1 month" and has undergone 3 cycles of chemotherapy. On this admission examination, the oral mucosa was scattered with irregular herpes (Figure 1A) Nikels' sign (+), multiple rashes on the surrounding skin (Figure 1B), the patient's skin lesions worsened after hormone therapy, some of them were seen to be ruptured and blister-like formation (Figure 1C, 1D). Hormones were increased and human immunoglobulin transmutation therapy was given, combined with the fact that the patient was in a low immune state after chemotherapy and had fever symptoms. The patient was highly suspected of having immune-related herpesvirus infection. The perfect herpes simplex virus and its special virus series antibody test showed that the IgG antibodies of herpes simplex virus 1 and herpes simplex virus 2 were positive, and the others were negative. The test result of pedestrian herpesvirus type 6 (HHV-6) in the outer hospital was reported as (-). We continued to ask about his medical history; the patient complained of oral Chinese medicine conditioning due to stomach discomfort in the past 1 month, 1 month ago (the third cycle of chemotherapy) the patient had back skin blisters. The rash disappeared after stopping the drug, and after continuing to take oral administration of the above Chinese medicine for nearly 5 days, a new rash appeared with rupture formation. In order to clarify the diagnosis, an ELISA test showed desmoglein1 (Dsg1) antibody > 150 U/mL (positive ≥ 20 U/mL). The results of a biopsy of the skin tissue of the right foot showed drug-induced pemphigus, immunofluorescence results: IgA (-), IgM (-), complement C3 (+), basement membrane granular), IgG (-) (Figure 1E, 1F). Symptoms improved after the addition of immunosuppressants. Diagnosis of DIP is based on history, clinical presentation, and laboratory findings.

**DISCUSSION**

Pemphigus is a rare and life-threatening autoimmune bullous disease marked by extensive flaccid blisters and erosions on the skin and oral mucosa. Many known triggers are associated with pemphigus, but medications remain the most prevalent cause of the disease. DIP is increasingly reported, and its mechanism is caused by a combination of biochemical interactions and abnormal stimulation by host B cells to produce intracellular IgG antibodies. These autoantibodies attack desmoglein and lead to cell separation within the epidermis leading to spinolysis [5,6]. Stimulant drugs can be classified according to their chemical structure, mainly mercaptans, phenolic drugs, and non-thiols/phenols. Thiol drugs are the most common cause of pemphigus because they contain sulfhydryl groups (-SH) in their chemical structure, which promote spinolysis by stimulating enzymes such as plasminogen activators, which break down keratinocytes and inhibit enzymes that promote the aggregation of keratinocytes. Phenol drugs disrupt the integrity of cell adhesion mechanisms by stimulating keratinocytes to release pro-inflammatory cytokines, such as cell release of tumor necrosis factor-α and interleukin-1 to drive complement and protease activation, which contributes to spinolysis. Non-thiols and nonphenols cause spinolysis by activating autoantibodies or altering the structure of target antigens on keratinocytes. Moreover, the incubation period of the disease varies from several days to months following the first intake of drugs to the onset of symptoms. In summary, DIP has many characteristics such as increased incidence, complex clinical mechanism, and long incubation period, which deserves the attention and vigilance of medical workers.

Here, we reported a case of DIP similar to herpes simplex in a lung cancer patient. Initially, the patient had scattered herpes on the skin and oral mucosa throughout the body. Combined with the patient's history of radiation oncology, being immunocompromised, and laboratory tests showing positive herpesvirus IgG antibodies, we highly suspected the possibility of herpesvirus infection. Then we performed HHV-6 test, but results were negative, and symptoms still did not improve after hormone booster treatment. We continued to follow up his medical history. The patient had a history of taking Chinese medicine. A complete histological examination and fluorescent staining was done, and finally a diagnosis of drug-induced pemphigus was made. It has been reported in the literature that long-term chemotherapy and radiotherapy for malignant tumors, long-term use of immunosuppressants, and biological agents for connective tissue diseases will lead to CD4+ T lymphocytes significantly lower than normal population. Their role in regulating immune cells and activating macrophages and other biological functions are significantly lower than normal, resulting in immunocompromised patients being susceptible to herpesvirus [7]. This patient has a history of recent chemotherapy for small cell lung cancer and belongs to an immunocompromised population. So, we highly suspected the possibility of herpesvirus infection in the early stage, and the advanced skin tissue fluid of patients with drug-induced pemphigus infection shows herpetic changes, which further increases the difficulty of distinguishing from herpes simplex [8]. Moreover, the positive early herpesvirus IgG antibody infection also misled our diagnosis. IgG is an immune protein, and its positive behavior mostly indicates previous infection with a certain type of virus, but it can be affected by a variety of factors, such as age, drugs, inter-
A Case of DIP Mimicking Herpes Simplex in Lung Cancer

Figure 1. Patient imaging and histological results.

On the first day of admission, irregular herpes and rashes on the oral mucosa and skin are scattered (Figure 1A, 1B). Skin lesions worsen after hormonal therapy and blister-like lesions appear (Figure 1C, 1D). Skin tissue light microscopy showed epidermal hyperkeratosis with dyskeratosis, subcorneal blister formation, blisters containing obvious spinous layer release cells, vacuolar degeneration and colloidal bodies in the basal layer (Figure 1E, 1F).

There are many commonly used diagnostic methods for DIP, including histological, immunological, 32-2B immunostaining [11], and in vitro γ-interferon release assays [12]. Some scholars believe that the identification of autoantibodies against the cell surface of keratinocytes is the "gold standard" for diagnosis [13,14]. The most widely used methods include DIF and IIF, immunoprecipitation, western blotting, and ELISA. Because the inducing drug can directly cause spinolysis through biochemical action rather than using immunological mechanisms, DIF and IIF have a certain misdiagnosis rate. ELISA is a very sensitive and specific method in patients with recombinant Dsg1 and desmoglein3 (Dsg3), which correlates well with clinical severity, and can be used for follow-up of patients, while western blotting and immunoprecipitation are more used for research due to their complexity and cost. 32-2B immunostaining has an irregular deposition of 87 percent in patients with idiopathic pemphigus, compared with only 30 percent in patients with DIP. In vitro γ-interferon release assays are more commonly used in exanthematous drug eruptions, severe drug eruptions, and drug-induced blister diseases. In summary, Maruani et al. [11] believe that the diagnosis of DIP needs to meet either one or both histopathological examinations. DIF examination under the condition of a history of oral suspicious drugs, and the drug has a precise connection with the disease and is consistent with the clinical characteristics of pemphigus. Histopathology not only helps determine the level of vesicular lysis but also distinguishes it from other subepidermal bullous lesions (Hailey-Hailey-like Grover disease and Hailey-Hailey disease, among others). Therefore, early perfect histopathological examination has important diagnostic value to clarify the nature of skin lesions.

The lesson learned from this patient's case is that even in herpesvirus IgG-positive blisters, the possibility of disorders other than herpes simplex should be consid-
ered in many ways, and histologic examination should be performed as early as possible to identify the type of lesion.

**CONCLUSION**

A positive herpesvirus IgG antibody is not a specific indicator of herpes simplex, and for patients with unexplained herpes, we should also consider the possibility of drug causes and improve histopathological examination as soon as possible to determine the specific cause.

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**Ethical Approval:**

This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in studies were in accordance with the ethical standards. Informed consent was obtained.

**Declaration of Interest:**

No conflicts of interest.

**References:**