Persistent Infection of Drug-resistant Influenza A Virus during Chemotherapy for Malignant Lymphoma

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Abstract

We herein report the case of an 80-year-old man with malignant lymphoma who became persistently infected with influenza A virus. Although he was repeatedly treated with NA inhibitors, such as oseltamivir or peramivir, nasal cavity swab tests for influenza A antigen continued to be positive for more than 2 months. Virological analyses revealed that he was infected with the NA inhibitor-resistant A (H3N2) virus possessing an R292K substitution in the NA protein. These findings suggest that a drug-resistant influenza virus strain might selectively survive antiviral therapy in elderly patients with refractory malignant lymphoma undergoing multiple chemotherapies.

Key words: persistent infection, influenza, malignant lymphoma, drug resistance

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Introduction

Influenza infection is usually self-limited. In the healthy adult population, the average duration of viral shedding is reported to be 4.8 days (1). Prolonged shedding, defined as seven days or more (2), can sometimes occur in childhood, elderly people and immunocompromised hosts, including patients with hematologic malignancy (3-9). Systemic glucocorticoid administration, diabetes or chronic lung disease can also impede viral clearance (4). In addition, several reports have previously warned that antiviral therapy may be associated with the emergence of drug-resistant viruses in such immunocompromised hosts with prolonged viral shedding (10-13). Furthermore, the drug-resistant AH3 subtype has rarely been documented during chemotherapy for refractory malignant lymphoma.

We herein report a case of malignant lymphoma that was complicated with a persistent infection of drug-resistant influenza A virus during chemotherapy.

Case Report

An 80-year-old man presented at our hospital because of fatigue and fever. He had a history of advanced gastric cancer about two years earlier, when he had undergone total gastrectomy and abdominal lymph node biopsy. Although the surgery for the gastric cancer was curative, the pathology of the abdominal lymph node, together with an additional biopsy specimen from a subcutaneous mass in the right upper arm, later revealed that he had diffuse large B-cell lymphoma (DLBCL) that had transformed from follicular lymphoma, stage III. He was given six courses of R-CHOP therapy [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (PSL)] and irradiation of a residual lesion on the right axillary, later revealed that he had diffuse large B-cell lymphoma (DLBCL) that had transformed from follicular lymphoma, stage III. He was given six courses of R-CHOP therapy [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (PSL)] and irradiation of a residual lesion on the right axillary, but the DLBCL soon relapsed in August 2014. Salvage chemotherapy included 2 courses of R-GDP therapy [rituximab, gemcitabine, dexamethasone and cisplatin] and 2 courses of R-B therapy [rituximab and bendamustine]. However, the disease was re-
fractory and another extranodal lesion in the right anterior chest wall developed. For the alleviation of symptoms, he was admitted to our hospital in December 2014.

He had a fever of over 38°C and a right anterior chest wall mass which measured about 10 cm in diameter. He had not received an influenza vaccination prior to the hospitalization. The fever was refractory to antibiotic therapies and it was considered to be a B symptom of malignant lymphoma. The influenza antigen was not examined at this point. The administration of PSL (30 mg/day) started in late December 2014 was palliative. At the beginning of January 2015, he received another round of chemotherapy with palliative intent, PEP-C therapy (PSL 30 mg, etoposide 50 mg, procarbazine 50 mg and cyclophosphamide 50 mg, given orally every other day). The chest mass decreased in size and the PEP-C therapy was discontinued because of cytopenia. PSL was continued at a dose of 20 mg/day.

In the middle of January, an outbreak infection of influenza A occurred in the hospital, when he was afebrile and a screening test for influenza A was negative, using a rapid chromatographic immunoassay. He was administered oral oseltamivir at 75 mg once a day for 5 days for prophylaxis. However, at the end of January, the patient became febrile, and another chromatographic immunoassay revealed he had been infected with influenza A. His complete blood count showed white blood cells of 5.40×10^9/L (neutrophils 89%, lymphocytes 3%, monocytes 7%), hemoglobin 8.5 g/dL and platelets 11×10^9/L. He was thus started on oral oseltamivir at a therapeutic dose: 75 mg twice a day for 5 days. The fever subsided quickly and he was discharged in early February. In the middle of February, the patient became febrile again and the antigen test of influenza A was found to be positive. He received an intravenous administration of peramivir at 300 mg. The fever went down quickly; however, the mass in the right anterior chest wall gradually increased in size. At the end of February, the patient was admitted to our hospital again because of pain and fatigue. His body temperature was normal, although the antigen of influenza A was still detectable. He underwent treatment for influenza including intravenous peramivir at 300 mg, followed by oral oseltamivir at 75 mg twice a day for 5 days. As a palliative measure, he continued to take the medications of PSL at 20 mg/day and etoposide, procarbazine and cyclophosphamide once a week for malignant lymphoma. He was under weekly surveillance for influenza virus shedding, using the same paper chromatographic immunoassay, yielding persistently positive results (Figure). As shown in Figure, while fever was occasionally observed, there were no respiratory tract symptoms, such as cough or sputum during the clinical course. His viral infection was poorly responsive to the antiviral therapies, while the lymphoma was refractory to anti-neoplastic therapies, and his general medical condition gradually deteriorated. The patient died in April 2015. Autopsy was not performed. No secondary infection of any drug-resistant influenza virus was documented among the other patients or the staff in the ward. The resistant strain...
Analyses related to influenza virus

Analyses related to influenza infection were performed. A genetic analysis showed the virus isolated from the patient to be an A (H3N2) subtype. Quantitative real-time RT-PCR analyses revealed the viral loads in mid- and late February to be 1.75 × 10^7 copies/mL and 9.04 × 10^6 copies/mL, respectively. Hemagglutination inhibition (HI) antibody titers to influenza virus in the patient serum in mid-February were as follows: A/California/7/2009 [A (H1N1) pdm09] was 1:20, A/New York/39/2012 [A (H3N2)] was 1:80, B/Massachusetts/2/2012 [B (Yamagata lineage)] was 1:10 and B/Brisbane/60/2008 [B (Victoria lineage)] was 1:10. From mid-February to mid-March, the antibody titer showed little change. Neuraminidase (NA) sequencing of the sample in mid-March revealed that the present strain had a known amino acid substitution associated with a reduced susceptibility to NA inhibitors: an arginine-to-lysine substitution at amino acid position 292 (N2 numbering, R292K) in the NA protein. The results of susceptibility testing by NA inhibition assay with fluorescent substrate are expressed as the drug concentrations required to inhibit the NA activity by 50% (IC50), as follows: oseltamivir 6,243.60 nM, peramivir 21.70 nM, zanamivir 3.87 nM and laninamivir 1.45 nM. This means that the present strain shows a highly reduced inhibition by oseltamivir and peramivir and a reduced inhibition by zanamivir.

Discussion

The present patient had several risk factors attributable to prolonged viral shedding, such as an advanced age, carrying malignant lymphoma, receiving anti-lymphoma therapies, lymphopenia and the administration of PSL, all of which might have led to an immunocompromised state that could hinder viral clearance (3-9). Furthermore, prolonged viral shedding and the long-term administration of anti-viral drugs may have provided a conductive growth environment for the drug-resistant viral strains (14-16). Thus, the NA inhibitor-resistant influenza A (H3N2) virus possessing an R292K substitution in the NA protein might have thus selectively survived in the present case with malignant lymphoma undergoing multiple chemotherapies. Utmost attention to the emergence of drug-resistant strains is warranted when the viral load does not decrease despite appropriate anti-viral medications.

Among the known NA inhibitor-resistant influenza A viruses, the most commonly detected amino acid substitutions are H275Y (N1 numbering) in A (H1N1) pdm09 viruses and E119V and R292K (N2 numbering) in A (H3N2) viruses (17). The H275Y mutant A (H1N1) pdm09 viruses had been detected sporadically (18), but a large cluster of such mutant viruses occurred in Japan during the 2013-2014 influenza season (19). In contrast, the detection of NA inhibitor-resistant A (H3N2) viruses was reported to be rare in the global antiviral resistance surveillance (20).

It is not clear when the present case acquired drug resistance because viral susceptibility testing was only performed once during the clinical course. However, drug-resistant viral strains generally have a less proliferative capacity than susceptible ones (21-25), so it might not have been detected even if a surveillance assay had been performed earlier. Although it is difficult to identify specific symptoms characteristic of the drug-resistant influenza virus in the present case, the lack of any respiratory tract symptoms per se might be a typical clinical feature of this strain.

Prolonged viral shedding despite anti-viral treatment, as observed in the present case, should draw clinical attention, and a high level of caution for the early detection of drug resistance is needed. Maximum precautionary measures should also be observed accordingly to prevent the further transmission of such viruses at medical facilities. It has been reported that mutant viruses show various degrees of impaired infectivity and transmissibility compared with wild-type strains (25). Such a compromised viral capacity may also explain our success in controlling an outbreak of any secondary infections in the ward.

In summary, it is necessary to inspect the drug resistance of the influenza virus, choose appropriate anti-viral agents and prevent transmission to other patients in cases where viral shedding persists.

The authors state that they have no Conflict of Interest (COI).

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References


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