



Fatal Chemotherapy-induced Combined Infection in a Hodgkin's Disease Patient: a Case Report

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Received: 09 May 2019 ♦ **Accepted:** 18 July 2019 ♦ **Published:** 31 Dec 2019

Citation: Kalchev YI, Lengerova GB, Asif U, Burnusuzov HA, Murdjeva MA. Fatal chemotherapy-induced combined infection in a Hodgkin's disease patient: a case report. *Folia Med (Plovdiv)* 2019;61(4):620-3. doi: 10.3897/folmed.61.e47811.

Abstract

Multimodal therapy, used for the treatment of patients with Hodgkin's disease (HD), makes them prone to life-threatening infections, attributed mainly to febrile neutropenia. Herein, we present a case report of fatal combined bacterial and viral infection in a 49-year-old female patient, subject to polychemotherapy for HD. Rapid microbiological diagnosis performed by multiplex polymerase chain reaction elucidated the causes of the infection within hours. *Listeria monocytogenes* was detected in both the cerebrospinal fluid and blood samples. Nasopharyngeal swabs returned positive for two swine-derived strains of influenza A virus. We aimed to emphasize the importance of these pathogens and draw attention to their association in the aetiology of infections among patients receiving chemotherapy. In conclusion, better surveillance is needed to improve the early diagnosis of infectious complications in these patients.

Keywords

febrile neutropenia, Hodgkin's disease, influenza A virus, *Listeria monocytogenes*, multiplex PCR

INTRODUCTION

Hodgkin's disease (HD) is a rare B-cells malignant disorder with an annual incidence in the USA of approximately 9000 cases.¹ It accounts for about 0.6% of all adulthood malignancies and is nearly 10 times less frequent than the non-Hodgkin lymphomas.² Combined chemotherapy used for the treatment of these patients makes them prone to life-threatening infections, attributed mainly to febrile neutropenia. Herein, we present a fatal combined listerial and flu infection of a female patient undergoing chemothera-

py due to HD. Our aim was to highlight the importance of these pathogens and draw attention to their association in the etiology of the infections among such patients.

CASE REPORT

A 49-year-old woman presented to the Emergency Department in a University Hospital in Plovdiv, due to extreme exhaustion and fever up to 38.5°C. This happened one week after receiving the second course of combined chemotherapy

(dose-escalating BEACOPP in cycles of 21 days with no drugs given on days 15–21) due to advanced HD, stage IV B (mixed cellularity subtype, verified by immunohistochemistry). She was admitted to the hospital initially sleepy and unresponsive, followed by psychomotor agitation. Over the next few days, her condition continued to deteriorate, with intractable fever up to 40°C. The impaired responsiveness gradually developed into a coma.

The laboratory blood tests demonstrated profound myelosuppression and elevated CRP. Serum protein and albumin levels were initially normal, transaminases and LDH were not more than 3 times the upper limit but the serum immunoglobulin levels were not tested. The patient was found to be negative for HIV, HBsAg, HCV (by ELISA tests) and TBC (T-Spot.TB test). Cerebrospinal fluid (CSF) was turbid and the evaluation showed pleocytosis with neutrophil predominance, hyperproteinorrhachia, hypoglycorrhachia and low CSF/serum glucose ratio (Table 1). The observed changes were typical for acute bacterial infection involving the central nervous system.

Multiplex PCR (FilmArray, Biofire, Biomerieux, Respiratory, Meningitis/Encephalitis, and Blood Culture Identification Panels) was used for microbiological assessment of throat swab, CSF and blood samples. The results were reported within several hours. Two strains of the influenza virus were detected in the pharyngeal swab: Influenza A H1 (2009) and Influenza A H3. *Listeria monocytogenes* was found from both CSF and blood samples. The bacterium was also confirmed by conventional microbiological methods. The antimicrobial susceptibility testing was performed by using the disk-diffusion method of Kirby-Bauer and EUCAST 2019 was used for interpretation. The bacterium showed sensitivity to all recommended antibiotics – ampicillin, benzylpenicillin, trimethoprim-sulfamethoxazole, meropenem, and erythromycin. The patient was set on oseltamivir due to the flu infection and ampicillin because of the *Listeria monocytogenes* for 5 days prior the lethal exit. Despite the rapid microbiological diagnosis and the initiated antimicrobial therapy, the patient died of acute circulatory and respiratory failure as a result of the listerial sepsis. The final diagnosis of listerial meningoenzephalitis with *Listeria monocytogenes* sepsis, Influenza infection, and Hodgkin's disease was established.

DISCUSSION

Multiple factors, including the clinical stage of the disease, the histological features, the presence or not of systemic symptoms, as well as the age, general physical condition, comorbidities and others, are considered when choosing the most appropriate treatment for the patients with HD.¹ Our case was considered 'advanced-stage' of HD (IV B), and the patient was set on six-cycles dose-escalated BEACOPP chemotherapy – bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone, and she was planned for treatment response assessment after the current second course, following the European Society for Medical Oncology's guidelines.³

Patients with HD have increased susceptibility to infections (bacterial, fungal and viral), due to functional B- and T cell defects.⁴ Low immunoglobulin levels and circulating normal B-cells, suppressed by the corticosteroid therapy, are one of the well-known mechanisms of immune suppression in oncological patients. Unfortunately the serum Ig levels and lymphocyte subpopulations (TBNK) were not tested in our patient. Recent studies suggest an important role for the CD4⁺CD25⁺Tregs, which are involved in the control of autoimmunity and transplantation, but can also suppress the effectiveness of the immune responses, including anti-tumor immunity. We realize that testing for these markers, which may contribute to a better understanding of not only the disease biology and prognosis, but the infectious complications as well, should be brought from bench to bedside and become routine in patients with HD.

The chemotherapy-induced leuko- and neutropenia predisposes to a variety of bacterial and viral infections as a complication and it is a major contributor to the morbidity and mortality. Febrile neutropenia is defined as a presence of fever (>38.5°C or >38.0°C in two consecutive readings for 2 h) and an absolute neutrophil count < 0.5×10⁹/L. The use of antibiotic prophylaxis in these patients is still debated due to the emergence of resistant microorganisms.⁵ For this reason, the rapid microbiological diagnosis is crucial for finding the aetiology and the very early initiation of a targeted antibiotic treatment.

Several observational studies found Gram (+) bacteria as the predominant cause of bacteremia in febrile neutropenic patients but higher mortality rates have been mainly associated with Gram (-) bacteria.^{6,7} *L. monocytogenes*

Table 1. Laboratory changes in an HD patient with a fatal combined infection

	HGB g/l	RBC ×10 ¹² /l	WBC ×10 ⁹ /l	PLT ×10 ⁹ /l	CRP mg/l	CSF cell count ×10 ⁶ /l	CSF protein g/l	CSF glucose mmol/l	CSF/ serum glucose ratio
Results	86 ↓	3.28 ↓	0.2 ↓	29 ↓	340 ↑	328 ↑	4.77 ↑	0.6 ↓	0.08 ↓
Reference	120-160	3.9-5.3	3.5-10.5	140-400	0-10	up to 5	0.15-0.45	2.2-3.9	0.4

is a Gram-positive, rod-shaped bacterium responsible for listeriosis in humans. These bacteria are ubiquitous in nature and found in soil, water, and can contaminate food.⁸ The bacterium does not pose a risk to healthy people but the immunocompromised individuals are prone to the infection, especially those receiving immunosuppressive chemotherapy.^{8,9} Bacteremia up to 74% and meningoen- cephalitis (21%) are the most common manifestations of listeriosis in those with depressed immune system due to hematological malignancies or chemotherapy, contributing to death in 75%.^{10,11}

Since the major 2009 pandemic caused by the novel swine-derived strain of Influenza A H1 2009, it continues to circulate and is responsible for local seasonal outbreaks.¹² The Influenza subtype A H3 was found to be predominant in the US feral swine population and also endemic in pigs in Asia and Europe, causing human infections.^{13,14} The association of these strains in the increased morbidity and mortality, especially in crucially ill patients and in those with chronic underlying diseases, is well documented.¹⁴⁻¹⁶ Undoubtedly, the involvement of these two strains of swine-flu mentioned has contributed to the severe clinical presentation and the outcome in our case. We were unable to find any other case report in the literature of such combined listerial and flu infection and to the best of our knowledge this is the first reported case.

CONCLUSION

In conclusion, the association of *Listeria monocytogenes* and Influenza viruses in patients with febrile neutropenia is possible. Listeriosis is an important infection in immunocompromised individuals, contributing to the morbidity and mortality. The clinical signs of listerial bacteraemia or meningoen- cephalitis are non-specific and should not be overlooked in patients with depressed immune system. Better surveillance is needed to improve infectious disease prevention and the outcomes in individuals subjected to chemotherapy.

ACKNOWLEDGEMENTS

Multiplex PCR tests (Respiratory, Meningitis/Encephalitis, and Blood Culture Identification Panels) used for the rapid microbiological detection were provided by two research projects of the Medical University of Plovdiv – grant No 09/2017 and No 05/2018.

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Фатальная форма двойной инфекции, индуцированной химиотерапией у пациента с болезнью Ходжкина: клинический случай

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Дата получения: 09 мая 2019 ♦ **Дата приемки:** 18 июля 2019 ♦ **Дата публикации:** 31 декабря 2019

Образец цитирования: Kalchev YI, Lengerova GB, Asif U, Burnusuzov HA, Murdjeva MA. Fatal chemotherapy-induced combined infection in a Hodgkin's disease patient: a case report. Folia Med (Plovdiv) 2019;61(4):620-3. doi: 10.3897/folmed.61.e47811.

Абстракт

Мультимодальная терапия, применяемая для лечения пациентов с болезнью Ходжкина (БХ), делает их восприимчивыми к опасным для жизни инфекциям, которые в основном связаны с фебрильной нейтропенией. Здесь мы представляем случай фатальной формы вирусно-бактериальной инфекции у 49-летней пациентки, проходящей полихимиотерапию по поводу БХ. Быстрый микробиологический диагноз, поставленный с помощью мультиплексной полимеразной цепной реакции, в течение нескольких часов выявлял причины инфекции. *Listeria monocytogenes* был обнаружен как в спинном мозге, так и в образцах крови. Носоглоточные мазки были положительными для двух штаммов вируса гриппа А, полученных от свиней. Нашей целью было подчеркнуть важность этих патогенов и привлечь внимание к взаимосвязи с этиологией инфекций у пациентов, проходящих химиотерапию. В заключение, необходимо повысить качество мониторинга для улучшения ранней диагностики осложнений от инфекции у этих пациентов.

Ключевые слова

Listeria monocytogenes, вирус гриппа А, болезнь Ходжкина, фебрильная нейтропения, мультиплексная ПЦР
