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Short Communication

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A Description of the Type, Frequency and Severity of Infections Among Sixteen Patients Treated for T-Cell Lymphoma

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Abstract

Background: Infections are an important cause of morbidity and mortality in T-cell lymphomas. Factors contributing to increased risk of infection include the nature of the underlying disease, as well as treatment-associated immunosuppression. Currently there are few reports describing the types of infections, including preventable infections, in this cohort of patients. The aim of the study was to identify the type, frequency and severity of infection in patients with T-cell lymphoma undergoing treatment.

Methods: A case series was performed on all patients with T-cell lymphoma over a 5-year period from 2011 to 2016 at a tertiary Australian hospital. Information was collected from medical record review regarding patient demographics, lymphoma treatment and outcomes, and infectious outcomes. Severe infections were recorded, defined as infection requiring hospitalization.

Results: Sixteen patients were identified with a diagnosis of T-cell lymphoma who received treatment at our institution. There were 42 discrete episodes of severe infections in total. Severe infections occurred in 81% of patients, with over 40% having more than one infection. The median length of hospital stay was 13 days, 33% required intensive care admission and 14% of infectious episodes resulted in death. Only 50% of infectious episodes were microbiologically proven, with the most common etiology being bacterial. The most commonly isolated organism overall was *Staphylococcus aureus*, with the most common source of infection being skin and soft tissue. There was one case of cytomegalovirus (CMV) infection and five cases (12%) of invasive fungal infection. The highest rates of infection occurred during progressive disease. Rates of prophylaxis were highest with antiviral agents, and comparatively lower with antibacterial and antifungal agents.

Conclusion: Infections are frequent, opportunistic and severe in patients with T-cell lymphoma. Our data suggests that fungal prophylaxis may be indicated with T-cell lymphoma.

Keywords: Infection; T-cell lymphoma; Type, frequency and severity

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Introduction

Mature T-cell non-Hodgkin's lymphomas (T-NHLs) are a rare and heterogeneous group of lymphoid malignancies that pose an infectious risk to patients both from direct perturbations of T-cell functionality, immune dysregulation and treatment related toxicities. Few studies exist that describe the types of infections in patients with T-cell lymphomas (Table 1) [1-24]. Identifying the types, timing and risks for infection may help guide clinicians deliver timely prophylaxis to protect against bacterial, fungal and viral infections.

The aim of this study was to describe the pattern of infectious episodes in patients with T-NHL in an Australian tertiary center to help inform infection prevention guidelines for patients undergoing treatment for T-cell lymphoma.

Materials and Methods

Study design and setting

We performed a retrospective cohort study at Monash Health, a 1,500-bed health service in Melbourne, Australia that treats approximately 150 patients with newly diagnosed lymphoma per year. All adult patients with a diagnosis of T-NHL by WHO 2008 criteria between January 1, 2011 and January 1, 2016

Table 1. Case Reports of Infections in Patients With T-Cell Lymphoma

Reference, year	Types of lymphoma	Organisms reported	Clinical details
Bacterial infections			
Fouillet (2018) [4]	Peripheral T-cell lymphoma	*Enterococcus faecalis*, *Strongyloides stercoralis*	*Enterococcus faecalis* meningitis, disseminated strongyloides. Patient died of secondary refractory status epilepticus.
Oeser (2015) [5]	Cutaneous T-cell lymphoma	*Mycoplasma pneumoniae*	Pneumonia. Patient recovered.
Umeh (2004) [6]	Cutaneous T-cell lymphoma	*Corynebacterium jeikeium*	Sepsis following experimental treatment with 8-methoxypsoralen photopheresis. Patient recovered.
Tauro (2000) [7]	Unspecified T-cell lymphoma	*Streptococcus pneumoniae*	Recurrent pneumococcal sepsis following splenectomy and bone marrow transplant. Patient recovered.
Mycobacterial infections			
Holik (2017) [8]	Angioimmunoblastic T-cell lymphoma	*Mycobacterium gordonae*	
Wekken (2016) [9]	Peripheral T-cell lymphoma, not otherwise specified	*Mycobacterium chelonae*	Disseminated infection, isolated in blood cultures.
Numbi (2014) [10]	Peripheral T-cell lymphoma	*Mycobacterium genavense*	Recurrent peripheral T-cell lymphoma and immunosuppressive therapy for seronegative arthropathy.
Artacho-Reinoso (2014) [11]	Lymphoblastic T-cell lymphoma	*Mycobacterium fortuitum*	Urinary tract.
Viral infections			
Nair (2011) [12]	Peripheral T-cell lymphoma	Herpes zoster	Disseminated - cutaneous, chorioretinitis. Patient died of progressive lymphoma.
Imafuku (2007) [13]	Angioimmunoblastic T-cell lymphoma	Varicella zoster	Disseminated cutaneous. Patient recovered.
Saito (2006) [14]	T-cell lymphoma - unspecified	Cytomegalovirus	Cutaneous, possible respiratory. Patient died of pneumonia.
Fungal infections			
Prakash (2017) [15]	Angioimmunoblastic T-cell lymphoma	Aspergillus fumigatus	Endophthalmitis. Patient died of fungal sepsis.
Tisi (2016) [16]	T-cell lymphoblastic lymphoma	Mucormycosis	Central nervous system involvement. Patient died.
Khan (2012) [17]	T-cell lymphoma - unspecified	Mucormycosis	Palatal involvement.
Powel (2012) [18]	Unspecified T-cell lymphoma	Cryptococcus uzbekistanensis	Bone marrow infection
Garcia-Noblejas (2011) [19]	Angioimmunoblastic T-cell lymphoma	*Pneumocystis jirovecii*, cytomegalovirus	Pneumonia. Patient died of infection.
Hsu (2006) [20]	Cutaneous T-cell lymphoma (mycosis fungoides)	*Fusarium spp.*	Cutaneous involvement. Patient recovered.
Poonawalla (2006) [21]	Cutaneous T-cell lymphoma (mycosis fungoides)	Coccidioidomycosis	Cutaneous and nodal involvement.
Parasitic infections			
Abdelrahman (2012) [22]	Angioimmunoblastic T-cell lymphoma	Strongyloides stercoralis	Disseminated Strongyloidiasis bacteremia. Patient died of infection
Stewart (2011) [23]	HTLV-1-associated adult T-cell leukemia/lymphoma	Strongyloides stercoralis	Disseminated - bowel, lung, skin. Patient recovered.
Isotalo (2000) [24]	HTLV-1-associated adult T-cell leukemia/lymphoma	Strongyloides stercoralis, Giardia lamblia.	Gastrointestinal involvement. Patient recovered.

HTLV-1: human T-cell lymphotropic virus type-1.

were included. Patients were identified through a search of hospital admission coding entries at Monash Health. Demographic data, details of lymphoma treatment and outcomes, and infectious outcomes were collected from medical record review.

Inclusion and exclusion criteria

Patients were identified from hospital coding and clinical databases and included if they had a hospital admission code for T-NHL first appearing during the study period. Patients were excluded if they were less than 18 years at time of diagnosis or the majority if their lymphoma care was not performed at the study institution.

Demographics

Demographic data collected at diagnosis of T-NHL included age, sex, country of birth, and comorbidities according to Charlson Comorbidity Index [25]. T-NHL specific staging and prognostic parameters included subtype of T-NHL, Ann-Arbor stage, International Prognostic Index (IPI) presence and sites of extranodal involvement, and date of first lymphoma admission [26]. Treatment received was recorded including type of chemotherapy (regimen type and duration), radiotherapy or observation for indolent T-NHL. Lymphoma specific treatment outcomes were recorded by standard response criteria, incorporating positron emission tomography (PET) where appropriate [27]. Supportive care was also recorded including use of prophylactic antibiotics, antiviral and antifungal agents, as well as use of granulocyte colony-stimulating factor (G-CSF).

Infectious outcomes

Severe infection was defined as any infection that required hospital admission and fulfilled the Common Terminology Criteria for Adverse Events (CTCAE) grade category 3, 4, or 5 [28]. For each episode of infection grade 3 or worse, data were collected regarding onset relative to last chemotherapy, dates and length of hospital admission. Method of acquisition of the specific infectious episode was recorded as community-acquired, hospital-acquired, or hospital-associated.

Data for microbiology isolates were extracted from the hospital laboratory information system. Infections were classified as "microbiologically proven" if microbiological organisms were isolated. If a site of infection was clinically evident but no microbiological organism isolated, the infectious episode was classified as "clinically defined infection". If no organism was isolated and there was no clear clinical source of infection, the infectious episode was classified as "fever without source". Details of each severe infection were recorded including presence of fevers or neutropenia. The absolute neutrophil count within 48 h of first day of the infectious episode was obtained from the laboratory information system. Neutropenia was defined as an absolute neutrophil count less than 1.0 $\times 10^9$/L [29]. Each severe infection was classified according to body site and these sites were not considered to be mutually exclusive. Sepsis was defined as the presence of systemic inflammatory response syndrome (SIRS) [30] with confirmed or presumed infection. Fungal infection was classified according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) [31]. Death due to infection or other causes at 30 days was recorded.

Statistical analysis

Descriptive statistics were used for incidence of infection, types of infection and changes over time. Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using median and standard deviation (SD) or median and interquartile range (IQR) as appropriate.

Ethics

This study was approved by the Human Research Ethics Committee at Monash Health as a quality improvement project (number 13085A). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Characteristics of T-cell lymphoma patients

Over the 6-year period, 16 patients were diagnosed with T-NHL and received their lymphoma management at the study institution. Sixteen patients were excluded (one patient was <18 years and the remaining 15 received their lymphoma care at another institution).

The demographic details of the patients are described in Table 2. The median age was 59 years and 10 (62%) were male. Fourteen (87%) received chemotherapy, and two patients died prior to commencement of chemotherapy.

Description of severe infections

Number of severe infections

Of the 16 patients, 13 (81%) experienced one or more severe infectious events. Six (37%) patients had one severe infection, three (19%) patients had two severe infections, one (6%) patient had three severe infections, and three (19%) patients had greater than four severe infections. There were 42 discrete episodes of severe infection in total. The median follow-up time was 1.93 years, and there was a median of 0.77 infections/year of follow-up.

Table 2. Demographics and Clinical Features at Study Entry (n = 16)

Demographics	Number (percentage)
Age (years)	59 (IQR 53 - 71)
Sex	
Male	10 (62)
Country of birth	
Australia	6 (37)
Europe	4 (25)
Asia	5 (31)
Oceania	1 (6)
Charlson Comorbidity Index	
1 - 2	3 (19)
3 - 4	7 (44)
5 - 7	6 (37)
International Prognostic Index	
0	4 (25.0)
1	3 (18.8)
2	3 (18.8)
3	4 (25.0)
4	1 (6.3)
5	1 (6.3)
Classification of T-NHL	
Peripheral T cell - PTCL-NOS	5 (31.3)
Angioimmunoblastic T cell	4 (25.0)
Anaplastic large cell	4 (25.0)
Enteropathy associated TCL	2 (12.5)
Stage	
I	0 (0.0)
II	4 (24.0)
III	3 (18.8)
IV	9 (56.3)
ECOG performance status point scale	
0	4 (25.0)
1	8 (50.0)
2	3 (18.8)
3	1 (6.3)
Types of chemotherapy	
First line	14 (87.5)
CHOP + variants	13 (81.3)
Other	3 (18.9)
Second line	4 (25.0)
ESHAC	3 (18.8)
IVAC	1 (6.3)
Brentuximab	1 (6.3)
Bortezomib	1 (6.3)
Romidepsin	1 (6.3)
Azacitidine	1 (6.3)
G-CSF prophylaxis	
Received	6 (37.5)

Data are presented as median/IQR or number and percentage as appropriate. IQR: interquartile range; T-NHL: T-cell non-Hodgkin lymphoma; ECOG: Eastern Cooperative Oncology Group; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; CHOP: cyclophosphamide, doxorubicin, vincristine prednisolone; ABVD: doxorubicin, belomycin, vinblastine, dacarbazine; PVM: procarbazine, vincristine, methotrexate; ESHAC: etoposide, carboplatin, cytarabine, methylprednisolone; IVAC: ifosfamide, etoposide, cytarabine; G-CSF: granulocyte colony-stimulating factor.

Timing of severe infections

Fifteen (36%) infectious episodes occurred during first line chemotherapy and two (5%) occurred during second line chemotherapy. Twenty-six episodes of infection (62%) occurred during progressive disease, 13 (31%) occurred during lymphoma remission, and three (7%) occurred during stable disease.

Clinical features of severe infections

Of the 42 severe infections, 21 (50%) episodes were microbiologically proven infections, eight (19%) were clinically defined infections, and 13 (31%) episodes were classified as fever without source. Seven (17%) episodes were community-acquired, 11 (26%) episodes were hospital-acquired, and 24 (57%) were hospital-associated. Thirty-four (81%) severe infections were characterized by fever. Twenty-three episodes of infection were defined from a clear source. The most common source of infection was skin with 10 episodes (24%), followed by lower respiratory tract with seven episodes (17%), upper respiratory tract with two episodes (5%), gastrointestinal with two episodes (5%), and urinary with two episodes (5%).

Twenty-one (50%) episodes had neutropenia associated with their infectious episode.

Description of microbiologically proven infections

Of the microbiologically proven severe infections, 13 (62%) were bacterial, three (14%) were viral, and five (24%) were fungal (Table 3).

Of the bacterial isolates, Gram-positive organisms accounted for seven (54%) and Gram-negative accounted for six (46%). *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most common Gram-positive and negative isolates, respectively. Six (46%) of the bacterial isolates were grown from blood cultures, of which two were taken from a peripher-

Table 3. Microbiologically Proven Infections in a Case Series of Patients With T-Cell Lymphoma (n = 16)

Organism	Number	Site
Bacterial (Gram-positive)		
Staphylococcus aureus	4	Wound swab (4), BAL (1), blood culture (1)
Streptococcus pyogenes	1	Blood culture
Coagulase-negative *Staphylococcus*	1	Blood culture
Enterococcus faecium	1	Blood culture
Bacterial (Gram-negative)		
Pseudomonas aeruginosa	2	Wound swab, urine MCS
Proteus mirabilis	1	Blood culture
Morganella morganii	1	Blood culture, urine MCS
Klebsiella pneumoniae	1	Sputum MCS
Enterobacter cloacae	1	Wound swab
Viral		
Picornavirus	1	Nasopharyngeal aspirate
CMV	1	Serum PCR
Influenza	1	BAL
Fungal		
Candida spp.	3	Liver biopsy (2), blood culture
Aspergillus fumigatus	2	BAL, sputum MCS

MRSA: methicillin-resistant *Staphylococcus aureus*; BAL: bronchoalveolar lavage; MCS: microscopy, culture and sensitivity; PCR: polymerase chain reaction; CMV: cytomegalovirus.

ally inserted central catheter line.

There were three (14.3%) viral isolates. CMV was isolated in one patient who was receiving valaciclovir anti-viral prophylaxis. The five episodes of fungal infection were found in three patients and included two episodes of hepatosplenic candidiasis, one episode of candidemia and two episodes of invasive pulmonary aspergillosis. Four of the five fungal isolates were classified as proven, and one was classified as possible according to EORTC guidelines [31]. Antifungal prophylaxis was not administered to these patients prior to diagnosis of fungal infection. There were no cases of *Pneumocystis jirovecii* pneumonia.

Severe infections and antimicrobial prophylaxis

Of the 16 patients, six were receiving viral prophylaxis (valaciclovir), three were receiving bacterial prophylaxis (two on trimethoprim-sulfamethoxazole and one on dapsone), and one patient was on fungal prophylaxis (fluconazole). The relationship between prophylaxis and severe infection is illustrated in Supplementary Material 1 (www.thejh.org).

Infection severity and death

The median length of hospital stay was 13 days (IQR 6.2 - 38). Fourteen (33%) episodes required intensive care unit (ICU) admission.

Of the 42 episodes of infection, 22 (52%) were classified as severe, and 14 (33%) life-threatening.

Within 30 days of the incident infection, eight (19%) patients had died, with four of these events attributed to complications from infection, and four events attributed to progressive lymphoma.

Discussion

This study demonstrated high rates of infection in patients with T-cell lymphoma with over 80% of patients experiencing severe infective episodes, and over 40% having multiple episodes of severe infection. A number of these infections were opportunistic and resulted in lengthy hospital admissions and/or death. The data indicate that further research could be directed towards infections prevention strategies in these patients.

There are few dedicated studies examining the type and severity of infections in patients with T-cell lymphoma. A list of case reports can be seen in Table 1, showing some common infections such as enterococcus, streptococcus and viral infections, but also a variety of atypical mycobacterial, fungal and parasitic infections.

In comparison to existing data, our cohort appears to have a higher rate of infective episodes [1] [1, 2]. In addition, the burden of fungal disease was high in our cohort at 24%, with only 2.4% of infective episodes being associated with fungal prophylaxis. No previous studies have specifically looked at

clinical rates of fungal infections in T-cell lymphomas, although a high rate has been described post mortem in patients with T-cell lymphoma by Suzumiya et al [3]. Additionally, local guidelines have identified these patients as low risk for invasive fungal infection [32]. According to our data, antifungal prophylaxis may be considered in some patients with T-cell lymphoma.

Our study identified that 50% of infective episodes were associated with neutropenia, while only 26% of infective episodes were associated with G-CSF use. This could perhaps suggest a role for increased monitoring and treatment of neutropenia to prevent infections; however, further information would be required to determine the true association and clinical benefit.

The episode of CMV raises the possibility that CMV monitoring may be indicated. Suzumiya et al performed a study on autopsy of patients with adult T-cell leukemia/lymphoma in 1993, and found the primary cause of death to be pulmonary infection, with CMV being the most common organism in 74.5% [3].

Study limitations include the retrospective nature of the study and the small number of T-cell lymphoma cases. We did not record the use of parenteral nutrition, which may influence infection rates.

Future research could focus on infection prevention through systematic screening and antimicrobial prophylaxis as a key strategy in the supportive care of patients diagnosed with T-cell lymphoma.

Conclusion

Our study, although small, demonstrates that there were high rates of proven fungal infection, and suggests that fungal prophylaxis may be indicated with T-cell lymphoma.

Supplementary Material

Suppl 1. The relationship between prophylaxis and severe infection.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

De-identified information was taken from medical records, therefore no informed consent was required.

Author Contributions

TK and CD devised the project and main conceptual ideas, developed the framework, and wrote the manuscript. TK and CS collected the data, TK analyzed the data. CD supervised the project. All authors discussed the results and contributed to the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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