

## CASE REPORT

### NK/T cell lymphoma associated with peripheral eosinophilia

Ernie YAP MD, Wan Fariza WAN JAMALUDDIN MBBS, MRCP, Nor Rafeah TUMIAN MD, MMed, Firdaus MASHURI\* MD, Fazarina MOHAMMED\* MBChBAO, TAN Geok-Chin\* MBBS, Noraidah MASIR\* MBChBAO, DPhil, and Fadilah S ABDUL WAHID MD, PhD

Cell Therapy Centre and \*Department of Pathology, Universiti Kebangsaan Malaysia Medical Centre, Malaysia

#### Abstract

NK/T cell lymphoma, nasal type is an aggressive and uncommon malignancy. Disease that occurs outside of the aerodigestive tract exhibits an even more aggressive clinical behaviour and does not respond as well to conventional therapy compared to its nasal counterpart. We report such a case of NK/T cell lymphoma, nasal type, that presented as an anterior chest wall mass, arising from the left pectoralis muscle. An interesting feature we wish to highlight is the associated eosinophilia that corresponded to disease activity, exhibiting fluctuations with surgical resection and chemotherapy. To the best of our knowledge this is the third reported case of NK/T cell lymphoma that is associated with peripheral eosinophilia. Our case highlights the role of certain NK cell subsets that play a major role in eosinophilic activation in NK/T lymphomas and calls for more research into further classification of this disease by virtue of its NK cell subsets.

**Keywords:** NK/T cell lymphoma, eosinophilia, extranasal

#### INTRODUCTION

NK/T cell lymphomas (NKTL) are aggressive malignancies. Although termed 'extranodal NK/T-cell lymphoma, nasal type', the 2008 WHO classification acknowledges that extranasal involvement is not infrequent; and both presentations are EBV-associated.<sup>1</sup> These extranasal sites include the skin, gastrointestinal tract, soft tissues and testis.<sup>2</sup> Most cases are disseminated at the time of diagnosis and the primary site is often difficult to elucidate.

The neoplastic cells are typically surface CD3-, cytoplasmic CD3ε+, CD56+, cytotoxic-molecule-positive, Epstein-Barr virus (EBV) positive, with germline T-cell receptor gene. They are invariably associated with EBV infection and EBER-positivity is a prerequisite for this diagnosis.

An international retrospective series<sup>3</sup> have shown that extranasal disease often exhibits a more aggressive clinical course and is refractory to current therapies. Furthermore, despite successful extrapolation of prognostic schemes such as the International Prognostic Index (IPI) from diffuse large B-cell lymphomas to nasal-type NK/T lymphomas, this has not shown to

be the case for extranasal subtypes, where the clinical outcome remains poor for all prognostic subgroups.<sup>4</sup>

Peripheral eosinophilia that is associated with NK/T cell lymphomas have been reported previously (Table 1). As NK cells have been shown to play a pivotal role in regulating eosinophilia *in-vivo*, this association may help sub-classify this heterogeneous disease by recognition of its NK cell subsets.

#### CASE REPORT

A 73-year-old man presented with an enlarging anterior chest wall mass over the last 7 months. The lesion started off at the size of a small coin, grew rapidly and was associated with pain. He had no fever, chills, pruritus, fatigue or weight loss. Except for a history of recently diagnosed Parkinson's disease and long-standing type 2 diabetes mellitus, he reported no other medical problems. His medications were carbidopa-levodopa, metformin and multivitamins, all of which he has been on for a while. He denied any skin rashes, allergic reactions or diarrhea.

On examination, there was a firm protruding anterior chest wall mass measuring 6cm x

**Table 1: Summary of case reports of peripheral eosinophilia associated with NK/T lymphoma**

Author, Year, Place	Patient's characteristic (sex, age)	Primary site	Disease stage	Treatment	Peak eosinophilia	Patient survival from diagnosis
Jin Ho Paik <i>et al</i> , 2010, Korea	Female, 52	Lower leg muscles	Advanced	Cyclophosphamide, doxorubicin, vincristine, prednisone, IT methotrexate	30%	26 months
Romero Fernández <i>et al</i> , 2011, Spain	Female, 21	Tonsils	Advanced	Cyclophosphamide, vincristine, dexamethasone, prednisolone	$1.99 \times 10 \text{ mm}^{-3}$	100 days
Ernie Yap <i>et al</i> , 2014, Malaysia (current report)	Male, 73	Pectoralis major	Advanced	Etoposide, cyclophosphamide, vincristine, dexamethasone, prednisolone	$1.7 \times 10^9/\text{L}$ / 42%	Alive; after 3 cycles of CHEOP; 5 months after diagnosis

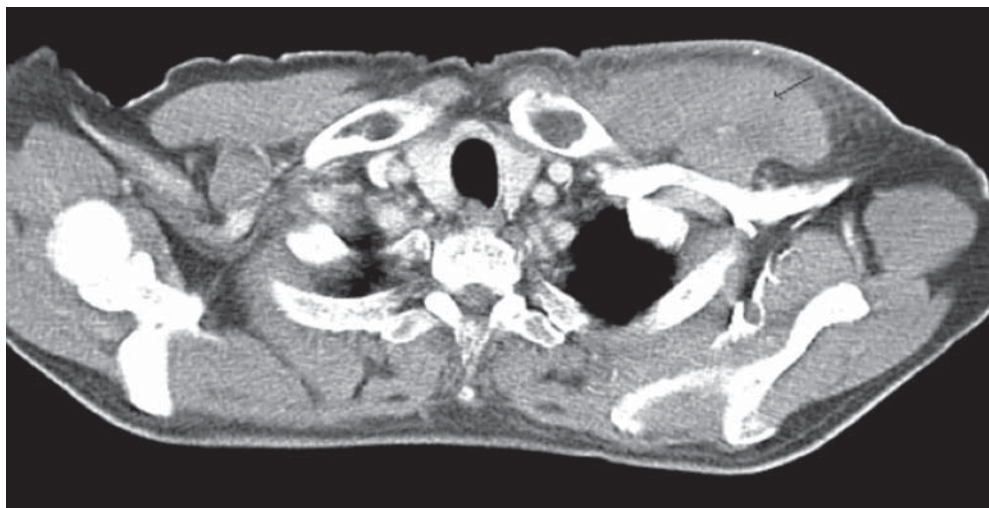
4cm x 5cm with erythematous overlying skin. There was no palpable lymphadenopathy and hepatosplenomegaly. He was not jaundiced. Aside from a resting tremor and mild cogwheel rigidity, the rest of the physical exam was not remarkable.

Laboratory investigations revealed a normal peripheral leucocyte cell count, with an increase in eosinophil count of  $1.7 \times 10^9/\text{L}$  (normal range 0.02-0.5), representing 42% of the leucocyte count. The hemoglobin level was at 12.5 g/dl

and his platelet count was  $142 \times 10^9/\text{L}$ . Lactate dehydrogenase (LDH) was 722 U/L (normal range: 211-423).

*Radiographic findings*

Computer tomography of the thorax, abdomen and pelvis was performed and showed a heterogeneously enhancing irregular mass involving the left pectoralis major muscle with infiltration into the subjacent subcutaneous tissue (Fig. 1) along with a well-defined hypodense



**FIG. 1:** Computer tomography of the thorax (transverse view): Heterogeneously enhancing irregular mass involving the left pectoralis major muscle with infiltration into the subjacent subcutaneous tissue (thin arrow).

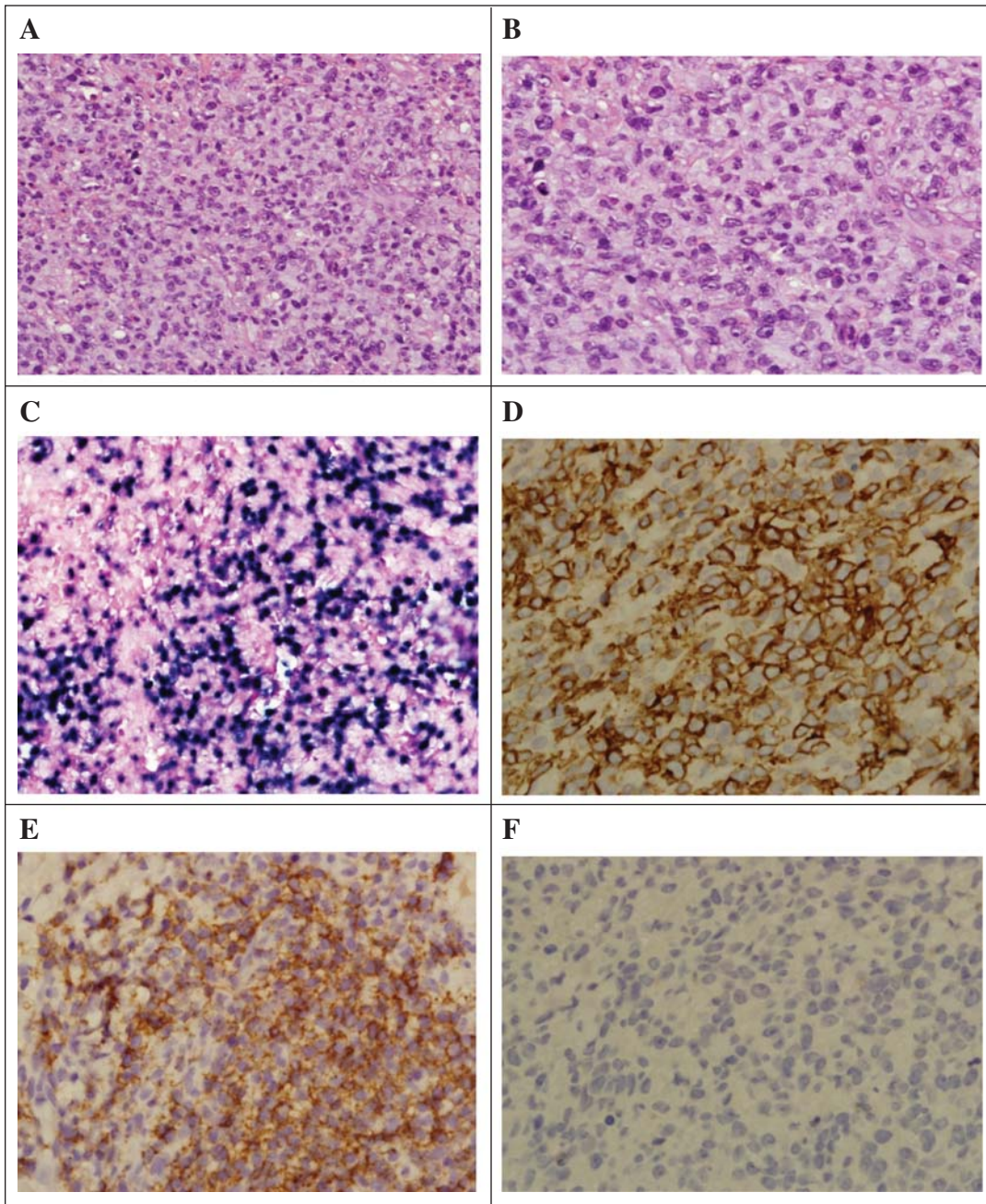


FIG. 2: (A) Histological examination of the skin lesion showed diffuse infiltration by malignant cells, admixed with lymphocytes and histiocytes at 20X magnification. (B) 40X magnification- an angiocentric and angiodestructive growth pattern with areas of necrosis were seen. Immunohistochemical staining shows the malignant cells are positive for EBV encoded RNA (C), CD30 (D) and CD56(E). Staining for CD20 (F) was negative.

lesion in the liver measuring 1cm in diameter and a pathological femoral fracture suggestive of metastatic disease.

*Pathological findings*

The patient underwent a wedge biopsy

of the chest wall lesion with appropriate immunohistochemical studies (Fig. 2). A bone marrow aspirate was negative for lymphomatous infiltration. The trephine biopsy did not yield adequate tissue for assessment.

Based on the above, a diagnosis of advanced



extranodal NK/T cell lymphoma of the musculature was established. The patient's ECOG performance status was rated at 1. His International Prognostic Index (IPI) Score was 4 (1 point each for extranodal sites, advanced stage, age, elevated LDH).

*Clinical course*

The patient was offered systemic chemotherapy with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHEOP) planned for 6 cycles with interim imaging, with his clinical condition and preference taken into consideration. Aside from a single episode of Grade 4 febrile neutropenia from which he recovered with antibiotics and granulocyte colony-stimulating factor, the patient has been tolerating this regimen quite well. Notably, the peripheral eosinophilia normalized with initiation of chemotherapy and coincided with clinical resolution of mass (Fig. 3).

Due to his advanced age and relative frailty,

it was decided that this patient was not a suitable candidate for high dose chemotherapy or hematopoietic stem cell transplant. At time of writing, after 3 cycles of CHEOP, the initial chest wall lesion has subsided and he is back to his baseline functioning level and free from symptoms. Further dose reduction of subsequent courses of chemotherapy was anticipated.

**DISCUSSION**

NK/T cell lymphomas that occur extra-nasally invariably are more chemo-resistant, exhibit a more aggressive clinical course that do not conform to conventional classification schemes based on host and tumoral factors.

Reports of NK/T lymphomas that are associated with peripheral eosinophilia are rare. In this report, we present such a case in an elderly patient who developed this disease in an unusual site. Notably, our patient's peripheral eosinophilia normalized in conjunction with tumour reduction.

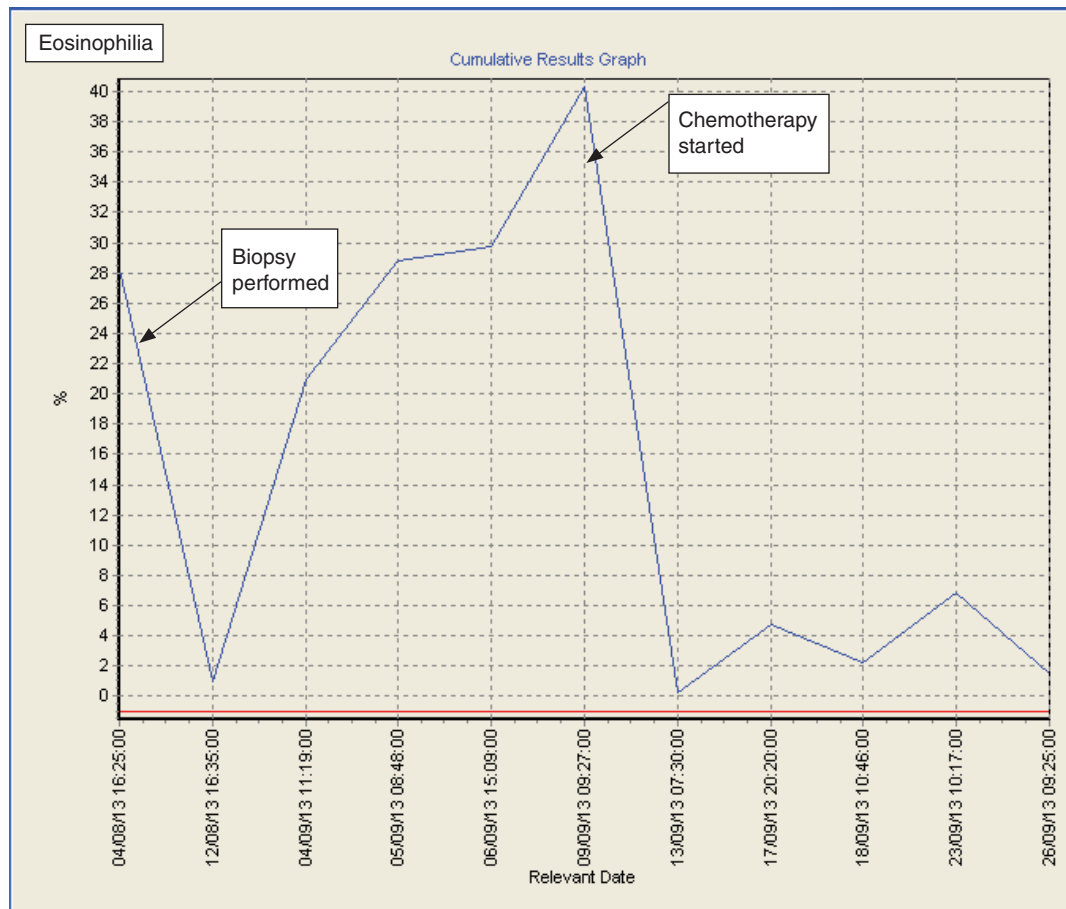


FIG. 3: Fluctuation of patient's eosinophilia in response to interventions.

Eosinophilia is in direct response to cytokines such as interleukin-2, granulocyte-macrophage colony stimulating factor and interleukin-5 (IL-5),<sup>5</sup> a Th2 cytokine, which are released in response to stimuli challenge such as parasitic infection or allergens. Peripheral eosinophilia has been associated with other lymphoid neoplasms. As part of the innate immune response system, it has been reported that certain subsets of NK cells may indeed produce IL-5.<sup>6,7</sup> Non-neoplastic NK cells have been shown to differentiate into at least 2 subtypes, with distinct physiological functions.<sup>8</sup> Indeed, certain subsets of NK cells are thought to play a central role in inducing eosinophilia in airway hypersensitivity reactions. It is conceivable that these specific histological subtypes of neoplastic NK/T cells may retain and/or augment these phenotypic manifestations due to deranged intracellular signaling pathways.

To our knowledge, eosinophilia associated with NK/T lymphoma has been sporadically reported (Table 1). One report described a 21-year-old patient presenting with hypereosinophilia and hemophagocytosis.<sup>9</sup> In another report, the authors described a patient with soft tissue swelling with peripheral eosinophilia who was initially diagnosed as Kimura's disease.<sup>10</sup> The authors proposed a viewpoint of understanding NK/T lymphomas from the perspective of NK cell subsets. As outlined above, NK/T lymphoma is thought to represent a heterogeneous group of related lymphomas and may be classifiable based on site of origin (nasal versus non-nasal) due to their distinct clinico-biological behaviour. However no attempts have yet been made to classify them based on histological subsets.

In conclusion, the above clinical vignette described a rare lymphoma with an unusual presentation, along with an intriguing association with peripheral eosinophilia. The significance of this is currently unclear but certain subsets of NK cells are known to regulate eosinophilia. Could this represent a subclass of NK/T lymphoma based on its NK cell subsets? Further observations along this perspective may be helpful.

#### ACKNOWLEDGEMENT

The authors have no conflict of interest to declare. This report was not supported by any funding agencies.

#### REFERENCES

1. Swerdlow SH. WHO classification of tumours

- of haematopoietic and lymphoid tissues. 4<sup>th</sup> ed. Lyon, France: International Agency for Research on Cancer; 2008.
2. Chan JK, Sin VC, Wong KF, *et al.* Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood.* 1997; 89(12): 4501-13.
3. Au WY, Weisenburger DD, Intragumtornchai T, *et al.* Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. *Blood.* 2009; 113(17): 3931-7.
4. Tse E, Kwong YL. How I treat NK/T-cell lymphomas. *Blood.* 2013; 121(25): 4997-5005.
5. Dubucquoi S, Desreumaux P, Janin A, *et al.* Interleukin 5 synthesis by eosinophils: association with granules and immunoglobulin-dependent secretion. *J Exp Med.* 1994; 179(2): 703-8.
6. Warren HS, Kinnear BF, Phillips JH, Lanier LL. Production of IL-5 by human NK cells and regulation of IL-5 secretion by IL-4, IL-10, and IL-12. *J Immunol.* 1995; 154(10): 5144-52.
7. Peritt D, Robertson S, Gri G, Showe L, Aste-Amezaga M, Trinchieri G. Differentiation of human NK cells into NK1 and NK2 subsets. *J Immunol.* 1998; 161(11): 5821-4.
8. Matangkasombut P, Pichavant M, Dekruyff RH, Umetsu DT. Natural killer T cells and the regulation of asthma. *Mucosal Immunol.* 2009; 2(5): 383-92.
9. Romero Fernández E, Pardo JRP, Doyle A, Albendea MC, de la Rúa AR. Hemophagocytic syndrome associated NK/T nasal type lymphoma presenting as hypereosinophilic syndrome: a case report and literature review. *Leuk Res.* 2011; 35(7): e97-9.
10. Paik JH, Jeon YK, Go HJ, Kim CW. Extranodal NK/T cell lymphoma accompanied by heavy eosinophilic infiltration and peripheral blood eosinophilia, involving skeletal muscles. *Korean J Pathol.* 2011; 45(Suppl 1): S70-4.