Review Article

Clinical Prediction Dilemmas of Non-Diagnosed Nasopharyngeal Hodgkin Lymphoma

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As a relatively uncommon disease in clinical practice, Hodgkin's lymphoma of the nasopharynx is particularly susceptible to misdiagnosis, which might delay treatment. Clinical dilemmas are regularly faced in the attempt to forecast this disease. With the aim of developing a flawless prediction system in the future to raise the rate of early diagnosis and enhance patient prognosis, we primarily highlight several dilemmas about tumor microenvironment, comparison of biopsy and surgery, and the usage of fluoro-2-deoxy-D-glucose positron emission tomography in this study. We summarized the predictive biomarkers in the Hodgkin's lymphoma microenvironment, including both routine and specific biomarkers such as mast cells, tumor related macrophages and so on. Fluoro-2-deoxy-D-glucose positron emission tomography is a highly useful method for the early diagnosis of Hodgkin's lymphoma. It can increase the accuracy and sensitivity of diagnosis and is also a valuable tool for therapy evaluation. Additionally, for pathological procedures, surgery is more dangerous but produces more accurate findings, whereas biopsy is less risky but produces less accurate results.

Key words: Hodgkin's lymphoma, nasopharynx, tumor microenvironment, biopsy, fluoro-2-deoxy-D-glucose positron emission tomography

Hodgkin's Lymphoma (HL) of the nasopharynx is often overlooked in clinical practice. According to previous literature, rarely HL can originate from the Waldeyer's Ring (WR) and just 0.32 % of all HL cases include the nasopharynx[1]. How to predict it by clinical clues is then indeed a question that needs to be explored. This review summarizes the previous literature to explore the clinical prediction dilemma before the diagnosis of HL in the nasopharynx from 3 aspects-tumor microenvironment, biopsy *vs.* surgery and Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET).

TUMOR MICROENVIRONMENT OF NASOPHARYNGEAL LYMPHOMA

Tumor microenvironment is a concept that combines tumor histomorphology and cell biology. It is made up of non-tumor cells, mesenchymal components, inflammatory agents, etc. The presence of neutrophils, lymphocytes and mast cells which are important elements of human immunity, in the tumor microenvironment is one of the key variables influencing tumor prognosis. Clinical doctors will make educated assumptions based on the peripheral blood inflammatory markers that are often assessed for the first time following hospital admission in clinical practice. According to the present biomarkers (Table 1), it is still challenging to forecast nasopharyngeal HL in time.

TABLE 1: BIOMARKERS IN THE TUMOR MICROENVIRONMENT OF HL

Group	Blood biomarkers
Routine	NLR
	LMR
	Mast cells
	Eosinophil
Specific	B cells
	PD-L1$^+$ and CTLA-4$^+$ T cells
	TAMs
	CCL17/TARC
	CD56$^+$ NK cells
	FGFs
	Eotaxin
	TNF-α

Note: NLR: Neutrophil to Lymphocyte Ratio; LMR: Lymphocyte to Monocyte Ratio; PD-L1$^+$: Programmed Cell Death Ligand 1$^+$; CTLA-4$^+$: Cytotoxic T Lymphocyte Antigen 4$^+$; TAMs: Tumor Associated Macrophages; CCL17: C-C motif Chemokine Ligand 17; TARC: Thymus and Activation-Regulated Chemokine; CD56$^+$ NK cells: Cluster of Differentiation 56$^+$ Natural Killer cells; FGFs: Fibroblast Growth Factors and TNF-α: Tumor Necrosis Factor alpha

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ROUTINE BLOOD BIOMARKERS

Peripheral inflammatory markers and nasopharyngeal lymphoma are both associated with the tumor microenvironment, but the relationship between them is unclear. However, a prior investigation found that the lymphocyte and monocyte counts might serve as a separate prognostic indicators for Diffuse Large B-cell Lymphoma (DLBCL)[2]. According to recent reports, Neutrophil to Lymphocyte Ratio (NLR) and Lymphocyte to Monocyte Ratio (LMR) are predictively significant in DLBCL patients[3]. Because Extranodal Natural Killer/T-Cell Lymphoma (ENKTCL) has a significant infiltration of Cluster of Differentiation 68^+ ($CD68^+$) mononuclear macrophages in its microenvironment, low LMR is associated with a poor prognosis and can be used as a risk factor on its own for the development of ENKTCL in the head and neck[4]. It is necessary to conduct more research to determine how neutrophils, lymphocytes, NLR and LMR relate to nasopharyngeal HL.

Although it has been demonstrated that mast cell numbers are linked to a poor prognosis in Classic HL (CHL)[5,6], it is uncertain if they can predict non-diagnosed HL. The level of angiogenesis in CHL corresponds with it[7] and it is significantly higher in nodular sclerosis HL than in other CHL subtypes[8,9]. Mast cells may be thought as a potential target for CHL adjuvant therapy since they prevent angiogenesis, impede tissue remodeling and promote the release of cytotoxic cytokines[10].

Through the production of pro-angiogenic substances, proteases that can alter stromal composition and tumor-promoting cytokines like Interleukin (IL)-10 and Transforming Growth Factor beta (TGF-β), mast cells have the potential to accelerate the formation of tumors[11]. Mast cells engage with CD30 ligand to activate Reed-Sternberg Cells (RSCs) cell lines *in vitro*, indicating that mast cells may induce carcinogenesis by directly interacting with RSCs and mast cells[12].

Mast cells contribute to the production of TGF-β and IL-13, which promotes fibrosis in CHL[13,14]. Toluidine blue staining, revealed mast cells in the fibrotic regions of the lymph node tissues from CHL patients. A strong positive connection was found between the incidence of fibrosis and the quantity of mast cells[13]. Compared to mice infected with RSCs alone, tumors forming in immunodeficient Non-Obese Diabetic/Severe Combined Immunodeficiency (NOD/SCID) mice implanted with mast cells are more fibrotic[15]. The quantity of mast cells positively linked with the incidence of fibrosis and TGF-β^+ mast cells were considerably more prevalent in nodular sclerosis CHL[13].

CHL often involves lymph nodes that exhibit eosinophilic infiltration symptoms. By promoting eosinophil production and recruitment to the area where CHL is active, cytokines and chemokines may be involved in this eosinophilia. In the bone marrow, IL-3, IL-5 and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) control eosinophilopoiesis[16]. IL-5 is particularly significant because it causes immature eosinophils to terminally differentiate, promotes the discharge of eosinophils into the blood and extends eosinophil lifespan. When it comes to CHL, tissue eosinophilia and IL-5 expression are correlated[17]. Eosinophils may be drawn by lymph nodes affected by CHL by chemokines as well. Eotaxin expression levels, a strong eosinophil recruitment factor are correlated with tissue eosinophilia in CHL[18]. Importantly, IL-13 can promote eotaxin production in fibroblasts and airway epithelial cells in a way that works in concert with Tumor Necrosis Factor alpha (TNF-α)[19,20]. Similar to this, enhanced eotaxin synthesis and eosinophil infiltration are brought on by *in vivo* amplification of IL-13 in the lung[21]. Thus, it is probable that IL-5 and eotaxin (through IL-13 and TNF-α) contribute in overlapping ways to the eosinophilia that is frequently observed in CHL.

SPECIFIC BLOOD BIOMARKERS

B cells and Tumor Associated Macrophages (TAMs):

Patients with HL, particularly those with CHL, frequently have lower absolute B cell counts in the tumor microenvironment[22]. In both early and advanced HL patients, Mulder *et al.* discovered a significant decline in the absolute numbers of B cells[23]. Additionally, there was a significant negative correlation between the proportion of B cells in the peripheral blood and lymph nodes and the proportion of B cells in the lymph nodes was significantly lower in patients with high tumor burden. Studies have demonstrated that anti-CD20 monoclonal antibodies can effectively treat HL, both in terms of treatment and prognosis[24].

As for TAMs, there may be a connection between RSCs and TAMs because CD163 expression in TAMs is associated with angiogenesis and decreased

survival in CHL[25]. There is an interaction between Programmed Cell Death Ligand 1$^+$ (PD-L1$^+$) tumor cells and Programmed Cell Death Protein 1$^+$ (PD-1$^+$) CD4 T cells and PD-L1$^+$ TAMs[26]. Shorter survival and the effectiveness of follow-up therapies are linked to increased CD68$^+$ TAM counts[27,28]. Monocytes are drawn from the blood by RSCs and healthy controls, which can also trigger a TAM M2 phenotype that inhibits cytotoxic T cells and draws in Regulatory T cells (Tregs) by secreting IL-10, IL-13, C-C Chemokine Receptor 5 (CCR5), TNF and GM-CSF[11]. High CD20$^+$ cells indicate a favorable prognosis for CHL, while they decrease together with an increase in TAMs defines a subset of individuals at high risk for the illness[28]. Then, it has to be confirmed if these two indications can function as predictors.

CD56$^+$ Natural Killer (NK) cells:

Low numbers of CD56$^+$ NK cells have been found in CHL and few studies have shown that NK function is dysregulated[29]. A higher percentage of arginase 1-positive Myeloid Derived Suppressor Cells (MDSCs) is significantly linked to a shorter progression-free survival time and a worse overall survival rate. Significant inhibition of circulating MDSCs is shown in CHL patients who responded completely and partially to the Phosphatidylinositol 3-Kinase gamma/delta (PI3Kγ/δ) inhibitor RP6530 in a trial[30]. Whether NK cells can be used as predictive biomarkers, needs to be further explored.

C-C motif Chemokine Ligand 17 (CCL17)/Thymus and Activation-Regulated Chemokine (TARC):

Since CCL17 (also known as TARC) is a known and clinically useful biomarker for CHL, Mulder *et al.* examined it by Enzyme Linked Immunosorbent Assay (ELISA) and anticipated to discover higher concentrations[23]. T helper 2 (Th2) CD4$^+$ T cells that express the CCR4, the CCL17/TARC receptor, are specifically attracted by CCL17/TARC[31]. The researchers also discover that the concentrations of CCL17/TARC are considerably greater in patients with a high tumor burden compared to those with a low tumor load. When the therapy is over, the levels of CCL17/TARC are restored to normal and stay there for another 6 mo. The suggested relationship between CCL17/TARC and metabolic tumor volume is supported by these data[32,33]. But further research is needed to determine whether CCL17/TARC can be a predictor of HL.

PD-L1$^+$ and Cytotoxic T Lymphocyte Antigen (CTLA)-4$^+$ T cells:

The latest study found that CHL patients displayed higher levels of proliferative T cells, higher concentrations of the circulating T cell markers, CTLA-4 and PD-1, and lower concentrations of naive T-cell frequencies in comparison to controls[23]. In patients compared to controls, larger percentages of CD4$^+$ and CD8$^+$ T cells expressed the inhibitory molecules PD-1 and CTLA-4, indicating that their T cells are exhausted. The proportions of CTLA-4$^+$ CD4$^+$ and CD8$^+$ T cells as well as the fractions of PD-1$^+$ CD8$^+$ T cells reduced after standard-of-care first-line therapy[23]. Accordingly, it appears that anti-PD-1 therapy combined with chemotherapeutic agents[34] and anti-PD-1 monotherapy[22] in HL patients reverses T-cell exhaustion. However, this raises the question of whether T-cell exhaustion is simply being treated by eliminating the tumor by any means rather than by any specific treatment or medication. Therefore, whether circulating T cells with high expression of PD-1 and CTLA-4 can be used as suggestive indicators needs further validation.

FIBROBLAST GROWTH FACTORS (FGFs)

Numerous human neoplasms, such as haematological neoplasia, have been identified to express FGF1 and FGF2 and their receptors. FGF can either directly or indirectly encourage the growth of tumors by encouraging the development of blood vessels. In 39 instances of HL, encompassing all subtypes and HL cell lines, Khnykin assessed the levels of FGF1 and FGF2 and FGF Receptors 1-4 (FGFR1-FGFR4). Majority of the time, the malignant cells were discovered to express FGF1 and FGF2 and their receptors FGFR2-FGFR4, but not FGFR1. It's interesting to note that the HL cell lines exclusively expressed FGFR3, not any FGFs or other FGFRs. This shows that while FGFs and the other FGFRs are activated *in vivo*, only FGFR3 is expressed constitutively by HL cells. Vascular Endothelial Growth Factor (VEGF), but not FGF, expression might be increased in Hodgkin's cell lines when cultured under hypoxic stress. FGF expression may be triggered by paracrine cues, in contrast to VEGF. It has been demonstrated in a subset of multiple myeloma that FGFR3 gene amplified or translocation

is the origin of constitutive FGFR3 expression; however, *in situ* hybridization failed to identify this. The Hodgkin's cell phenotype may include the expression of FGFR3. Given that FGFs and several of their receptors are widely expressed in HL, it is likely that FGFs are crucial for maintaining the development of the lymphoma and those anti-FGF antibodies may be utilized as an adjuvant therapy.

Eotaxin:

By using RT-PCR, it was shown that CHL tissues express more eotaxin than healthy lymphoid tissues do[18]. Elevated eotaxin expression was predominantly linked to nodular sclerosis CHL instances within CHL subtypes. In CHL tissues, eotaxin was found by immunohistochemistry in RSCs; nodular sclerosis CHL patients exhibited more pronounced staining than mixed cellularity CHL cases. Additionally, there was a correlation between the expression of eotaxin and the quantity of eosinophils in the CHL tissue, indicating that eotaxin aids in eosinophil recruitment to CHL tissues. In contrast to these results, only 1 out of 5 RS cell lines had eotaxin messenger Ribonucleic Acid (mRNA) identified by Jundt *et al.* They were also unable to identify eotaxin expression in primary RSCs[35]. They discovered that macrophages contributed little to the production of eotaxin and that fibroblasts were the main source. By separating co-cultured RSCs from cultivated fibroblasts using a micropore membrane, it was possible to promote the expression of eotaxin, demonstrating that soluble factors created by the co-cultured RSCs encouraged the up-regulation of eotaxin expression. High quantities of TNF-α[36], a cytokine known to promote eotaxin synthesis are produced by the RS cell line L-1236. Studies on the neutralization of TNF-α by antibodies revealed that this cytokine was mostly in charge of inducing the synthesis of eotaxin in fibroblasts co-cultured with L-1236 cells.

TNF-α:

TNF-α was first discovered to be a macrophage product that mediated cytotoxicity against specific cell types, particularly altered cell lines. TNF-α has since been demonstrated to have significant roles in tissue remodeling, inflammation and wound healing[37]. TNF-α increase the phagocytic and microbicidal functions of macrophages and promotes the production of IL-1 and IL-6, among other proinflammatory cytokines. TNF-α expression at the mRNA and protein levels in relation to CHL has been shown in 7 RS cell lines. TNF-α was identified by Northern analysis in all 19 instances of CHL that were examined[38] by immunohistochemistry or *in situ* hybridization in primary RSCs in 69 % of the cases of CHL that were studied[39-44]. Additionally, TNF-α is the reactive infiltration contained lymphocytes and macrophages. TNF-α may utilize the TNF Receptor type I (TNFRI) (p55) and type II (TNFRII) receptors (p75). Out of 60 only a few primary tumors and RS cell lines had any research on these receptors. Ryffel *et al.* employed immunohistochemistry to look at the expression of TNFRI and TNFRII in malignant lymphomas, including 4 instances of CHL. One instance of CHL and two cases of CHL both had TNFRII RSCs[45]. The RS cell lines treatment recombinant TNF-α with Hodgkin's Disease Derived cell line (HDLM-2) and Hodgkin's Reed-Sternberg cell line (KM-H2) did neither promote nor prevent cellular growth.

FDG-PET:

Patients with nasopharyngeal masses should often have an enhanced Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI). Due to its high cost and infrequent usage in clinics without proof of probable metastasis, FDG-PET is a highly costly imaging technique. Only five publications that investigated FDG-PET for HL including WR were found in the literature review[46]. The significance of performing FDG-PET, however, is becoming clearer as the technology develops. A false-positive diagnosis of patient involvement in these regions may result if a physical examination or CT/MRI is used in parallel without the use of FDG-PET for metabolic assessment. The anatomical and metabolic activity of the nasopharyngeal area can be evaluated with a combination of FDG-PET and CT/MRI while lowering the possibility of false positive results[47,48].

Hutchings *et al.* discovered that FDG-PET significantly outperformed enhanced scans alone in terms of sensitivity for the first stage of HL in the adult population[49]. This was especially clear in the extra-nodal region, where FDG-PET demonstrated a sensitivity of 86 % as opposed to 37 % for enhancement CT alone.

When it comes to the examination's timing, it may often be carried out after enhanced CT/MRI of the cervical lymph nodes and ultrasound of the neck indicate anomalies in the nasopharynx that cannot be conclusively identified, before biopsy or surgery[46].

On the other hand, some patients have undergone a biopsy or surgery to clarify the pathology for a variety of reasons. In these cases, it is still required to do a FDG-PET after surgery to determine whether the lesion is situated elsewhere in the body[50].

Recent research have also demonstrated that FDG-PET can serve as a prognostic sign for HL in its early stages[51-53]. According to Cottereau *et al.*, Total Metabolic Tumor Volume (TMTV) enhanced baseline risk classification of patients with early-stage HL compared to the present staging system and FDG-PET as a measure of total tumor burden better-identified individuals at high risk for the disease[51]. Additionally, it increases the early FDG-PET response's predictive value.

Due to its accuracy, sensitivity, predictability and role in therapy guidance, FDG-PET is a valuable diagnostic tool. The clinician should continue to consider using FDG-PET as a routine diagnostic tool in case of undiagnosed HL.

Biopsy or surgery:

The most accurate way to diagnose HL is still through pathology. Clinicians continue to struggle with the decision of whether to obtain pathology specimens during surgery or biopsy. Only 7 pathology specimens were obtained intraoperatively in a prior report and the rest were obtained through biopsy[54]. Biopsies have the benefit of being less invasive and risky, but they are also prone to false negatives. According to Biorklund *et al.*, an otolaryngologist thoroughly examined and then performed biopsies in 45 adult HL patients[55]. Only 7 patient's nasopharyngeal abnormalities were visible on endoscopy, while the majority of patients had no abnormalities. The high rate of false negatives on nasopharyngeal biopsy prompted the recommendation of extended biopsy for the diagnosis of HL, while tonsils that were also seen in WR followed a similar trend. 87 individuals who had tonsillectomy for clinical tonsillar asymmetry without radiological or other indications or symptoms of cancer were examined for their pathology[56]. In these 87 individuals, only 2 malignancies (2.3 %), 1 HL and 1 non-HL were discovered. These studies highlight the unreliability of physical examination, direct endoscopy and local biopsy as indicators.

The most latest diagnostic criteria for HL require a biopsy to diagnose the condition[57]. However, fine needle aspiration or coarse needle aspiration biopsies are insufficient. The benefit of surgery is that specific lesions can be entirely removed, resulting in more accurate pathology findings and faster symptomatic response. HL is a unique malignancy with a minority of tumor cells in the cell population and inadequate biopsy may not be able to include malignant cells in the specimen, so surgery is more appropriate for nasopharyngeal masses with isolated lesions that are easily excised. However, the drawback is that it is more dangerous and intrusive than biopsy surgery. In the majority of prior cases[55,56], the need for a biopsy was driven by the possibility of lymphoma, the presence of multiple lesions, surgical trauma or involvement of significant neurovascular lesions and technical challenges during surgery. Therefore, before diagnosis of HL, the physician must weigh the advantages and disadvantages of surgery *vs.* biopsy.

CONCLUSION

As a rare disease, nasopharyngeal HL is difficult to diagnose clinically. However, with the development of biomarker systems, advancements in imaging technologies including FDG-PET and advancements in endoscopic technology, nasopharyngeal HL can now be identified at an early stage and treated according to standard protocols to improve prognosis.

Conflict of interests:

The authors declared no conflict of interest.

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