Editorials
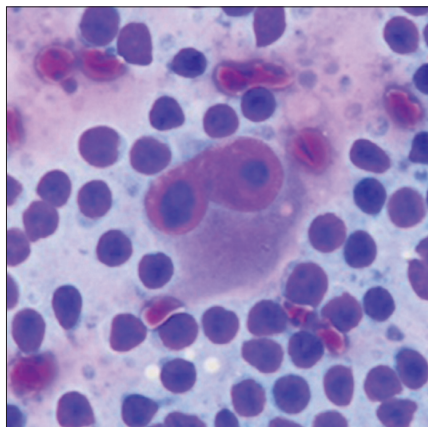
Assessing risk and improving survival in lymphoma

INTRODUCTION

Lymphoma represents the sixth most common form of cancer in the UK, with non-Hodgkin lymphoma (NHL) representing 4% and Hodgkin lymphoma (HL) <1% of cases; over 13 000 lymphoma cases are diagnosed annually[1,2] and its incidence, in particular NHL, has continued to rise over recent decades.[3] There are now more than 40 recognised lymphoma subtypes and this contributes to its heterogeneity of clinical presentation, ranging from subtle signs and symptoms to acutely unwell cases with end-organ compromise.

The recently reported Eurocare-5 study[4] addressed composite data from 30 cancer registries across Europe, including the UK, and demonstrated improvements in 5-year adjusted survival for HL and subtypes of NHL, including the two most common: diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). However, the overall 5-year survival rate for NHL in the UK (57.4%) was inferior to the European mean (59.4%),[5] so there is a pressing need to address this disparity and the factors that may be responsible.

Without the signs of a classical lymphoma presentation, patients will often visit their GP many times[6] before a possible diagnosis comes to light, often resulting in delayed referral and diagnosis. Therefore, knowledge of the common signs and symptoms is crucial and may help guide GPs to recognise the disease earlier, refer on appropriately, and avoid unnecessary diagnostic delays. The final diagnosis of lymphoma always requires histological confirmation and appropriate staging investigations. The sooner this is performed, the more likely

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patients will be treated at the earliest possible stage of their disease, conveying a better prognosis. The National Institute for Health and Care Excellence (NICE) lymphoma referral guidelines[7] can be found under the section of haematological cancers and first lists general recommendations that include a combination of symptoms and signs, which may suggest a haematological cancer and warrant further investigation. These guidelines help GPs expedite referral to hospital specialists in the secondary care setting. The 2-week wait rule allows patients urgently to be reviewed within 2 weeks of referral by a secondary care provider. Patients with a particular combination of signs and symptoms with reference to the presentation of lymphoma are recommended for urgent referral, however the ranking and importance of each particular symptom and sign is not readily conveyed.

OPTIMISING ASSESSMENT OF CLINICAL RISK FACTORS

In this issue, Shephard and colleagues report two large case–control studies that determine symptom and sign risk profiles for patients in the primary care setting who go on to develop NHL ($n = 4362$)[8] or HL ($n = 283$),[9] respectively. This is the first approach of this scale performed in the primary care sector to address the presenting features of lymphoma. Both are systematic and well designed, taking a similar approach to quantify the diverse symptoms with which the lymphomas

can present. Data from more than 680 general practice surgeries across the UK included in the Clinical Practice Research Datalink (CPRD) were used in a manner analogous to previous solid cancer studies reported by this group. A comprehensive series of symptoms and investigations were considered, multivariable analysis performed, and a set of variables which confer risk of NHL or HL was determined through positive predictive values (PPVs).

When results from the studies are taken together, PPVs for developing NHL or HL in patients aged ≥60 years include: 18.6% for the presence of lymphadenopathy, 4.6% for a head and neck mass, and 1.1% for a mass found elsewhere in the body. A clear message emerges, namely that unexplained lymphadenopathy, particularly in older patients, could reasonably lead to an immediate decision to refer onwards to specialist lymphoma diagnostic services and builds on existing NICE guidance.[7] While abnormalities of simple blood tests (affecting full blood count, inflammatory markers, liver function tests, and gamma globulins) helped refine the risks, the absence of such changes cannot exclude lymphoma. Furthermore, the doubling of primary care consultations in the year before diagnosis for patients that go on to develop lymphoma is striking. This sets the challenge as to whether early recognition of this trend may be used, perhaps in tandem with the alert symptoms and signs, to help further risk stratify cases in the primary care setting and guide onward referral.

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The reported low incidence of B symptoms (weight loss 4%, excessive sweating 1.2%, and fever 1.2%) in the NHL study[8] contrasts to higher frequencies reported in studies of aggressive NHL (41%[10]) and indolent NHL (FL, 19%[11]) and those observed in our personal experience. A similar low level of such systemic symptoms in the HL report[9] contrasts with the international prognostic collaboration report of 71%.[12] It seems probable that these differences reflect the combination of the typically later presentation to secondary care in the course of disease that can sometimes provide time for such symptoms to develop, and the active pursuance of these somewhat non-specific symptoms being precipitated when a diagnosis is either strongly suspected or proven in the secondary care setting.

FUTURE DIRECTIVES

Whether integrating active screening for B symptoms — as well as for rarer symptoms such as generalised pruritus, a feature which although not a classical B symptom may be observed in patients who present especially with classical HL (authors personal clinical observations) — to help to refine the primary care symptom profile for NHL and HL to further aid GPs to suspect a diagnosis of lymphoma and expedite early referral to specialist services, is a question that could be addressed in future studies. The historical reports indicating GPs are able to distinguish malignant from benign lymphadenopathy are important and the PPVs determined for masses in older patients by Shephard's group develop this further.[8,9] However, this should be considered in the context of recent developments in national referral practices including the cancer (2-week wait) referral pathway from which only a relatively small proportion (in the region of 10% in our centre) of suspected lymphoma referrals prove to be either NHL or HL. While Shephard *et al*'s studies could not specifically address size from the CPRD data, lymphadenopathy ≥2 cm or rapid enlargement should be considered as urgent red flag signs and prompt referral would be judicious. Such disease presentation characteristics may help inform the referral pathway but age itself remains a particularly important predictor of survival in lymphoma.

The Eurocare-5 report[4] indicates that 68% HL occurs in the 15–54-year-old population in the UK; a seemingly younger patient population from cancer registry data than that provided from CPRD data in the accompanying report. This may reflect differing patient flows to diagnosis across varying age demographics and may contribute to the generally lower PPVs across the three mass variables (lymphadenopathy, head and neck, and other) observed for HL compared to NHL. Nonetheless, risk estimates for cases aged ≥60 years provided in the reports are important, as HL survival is consistently inferior for older cases and earlier referral for specialist review may help abrogate this phenomenon. Similarly, the outcomes for older patients with NHL lag behind those who are younger and the age distribution for NHL in the report by Shephard *et al* (78.5% of NHL occurring in ≥60-year-olds[8]) is consistent with Eurocare-5 (60% in the ≥65-year-old population and 80% in ≥55-year-olds).[4] The similar age demographic further validates the symptom profile in NHL with its attendant PPVs, supporting the early referral of such cases.

The studies by Shephard and colleagues[8,9] provide an important insight in to the presentation of NHL and HL in the primary care setting and can be used to inform referral practices, most notably in older patients. In tandem with the studies' insights, a specialised learning tool dedicated to the subject of lymphoma in the primary care sector has been produced by the Royal College of General Practitioners and the Lymphoma Association and should be a valuable resource.[13] The challenge remains to demonstrate whether the upfront risk stratification of symptoms demonstrated by Shephard and colleagues can facilitate earlier presentation to specialist diagnostic services and, ultimately, contribute towards further improvements in the outcome of NHL and HL.

Paul A Fields,
Consultant Haematologist, Department of Haematology, Guys and St Thomas' Hospitals, London.

David J Wrench,
Consultant Haematologist, Department of Haematology, Guys and St Thomas' Hospitals, London.

ADDRESS FOR CORRESPONDENCE
Paul A Fields
Department of Haematology, 4th floor, Southwark Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK.

E-mail: Paul.Fields@gstt.nhs.uk

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