

Staging for CLL-type non-Hodgkin's lymphoma reveals a gastrointestinal stromal tumour

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ABSTRACT

We report a 73-year-old man presenting with fatigue, lymphadenopathy and weight loss. He had no abdominal pain, fever or night sweats. Physical examination revealed a palpable 1.4-cm hard nontender lymph node behind the left sternocleidomastoid muscle and a palpable 2-cm lymph node in the left axilla. Bone marrow examination and excisional biopsy of the lymph node behind the left sternocleidomastoid muscle showed a CLL-type non-Hodgkin's lymphoma (CLL-type NHL). Staging by CT scanning revealed, besides axillary and mediastinal adenopathy, an unexpected mass in the stomach. Gastroscopy and pathological evaluation showed a gastrointestinal stromal tumour (GIST) with immunohistochemical staining for CD 34 and CD 117. The patient was treated with imatinib. CLL-type NHL and GIST both tend to occur in middle-aged and older patients. A double-tumour consisting of both these tumours is rare: the incidence is estimated to be 3 per 10 billion people.

INTRODUCTION

A CLL-type non-Hodgkin's lymphoma (NHL) is a neoplasm that usually occurs in middle-aged and older patients (aged 40 to 80 years). The incidence in the age category above 60 years is 20 per million people.¹ Gastrointestinal stromal tumours (GISTs), although relatively rare (0.1 to 3% of all gastrointestinal neoplasms), are the most common mesenchymal tumours of the gastrointestinal tract. They usually occur in the stomach (60%), with the remainder in the small intestine (15%) and other sites, including large bowel,

oesophagus, rectum, mesentery and omentum. They also tend to occur in middle-aged and older adults, with a slight predilection for men. The approximated incidence in the Netherlands is 16 per million people.²⁻⁵

We report a male patient with a NHL and a GIST at the same time. This double-tumour is rare and, as far as we know, has never been described before. The approximated coincidence of these tumours is, on the basis of their presumed independent incidences, 3 per 10 billion people.

CASE REPORT

A 73-year-old man presented with fatigue, lymphadenopathy and weight loss. He had no abdominal pain, fever or night sweats. On physical examination he had a palpable firm nontender lymph node with a diameter of 1.4 cm behind the left sternocleidomastoid muscle and a palpable 2-cm lymph node in the left axilla. No other abnormalities were found on physical examination. Laboratory examination revealed an erythrocyte sedimentation rate of 4 mm, haemoglobin 5.7 mmol/l, leucocytes $5.6 \times 10^9/l$ with normal differentiation, thrombocytes $249 \times 10^9/l$, albumin 33 g/l and ferritin 6 $\mu\text{g/l}$. Glucose, minerals, liver enzymes, lactic acid dehydrogenase, bilirubin, thyroid stimulating hormone, vitamin B12 and folate were normal and no M-proteins were found.

Bone marrow examination showed a diffuse infiltration of a small lymphocytic NHL. Histological examination of the lymph node behind the left sternocleidomastoid muscle revealed a CLL-type NHL with positive immunohistochemical staining for CD 20 and CD 5; CD 23 was not

clearly positive, which is unusual. Molecular examination showed karyotype 47 XY +12, which is typical for CLL-type NHL.

Staging by CT scanning of the thorax and abdomen revealed, besides axillary and mediastinal adenopathy, an unexpected mass in the stomach (*figure 1*). Gastroscopy showed a tumour in the stomach. Pathological evaluation showed a GIST with immunohistochemical staining for NSE, CD 39, CD 34 and KIT (CD 117) in the cytoplasm of the abnormal cells.

A complementary positron emission tomography (PET) showed high activity in the stomach, characteristic of a malignancy of the stomach and positive axillary and mediastinal regions as can be seen in lymphoma.

The patient was treated with imatinib. Gastric resection was not performed because of the predicted high morbidity due to the coexistent NHL. The follow-up of the NHL consisted of observation. After one month of treatment with imatinib the PET scan showed regression of the activity in the stomach.



Figure 1
CT of the abdomen showed a gastrointestinal stromal tumour

DISCUSSION

Patients with a CLL-type NHL usually present with persistent painless generalised lymphadenopathy. The peripheral blood may be normal or reveal only a mild lymphocytosis. M-proteins are found in 20% of the cases. Patients can often be observed without treatment for three to four years. The median survival is eight to ten years.¹ Patients with a GIST may present with a variety of symptoms such as vague abdominal pain, gastrointestinal

bleeding, fever, night sweats and weight loss.²⁻⁵ GISTs range from small indolent tumours curable with surgery alone to aggressive metastatic cancers. Predicting the clinical behaviour of a newly diagnosed GIST is difficult in the absence of frank neoplastic spread.⁶

GISTs express CD 34 (approximately 70% of cases) and KIT (CD117), a transmembrane tyrosine kinase receptor that is the protein product of c-kit proto-oncogene (up to 100% of cases). Most GISTs have a mutation in the c-kit proto-oncogene that translates into a gain-of-function constitutive activation of KIT. KIT activation seems to play a central role in GIST pathogenesis, seemingly serving as a requisite for neoplastic behaviour in the majority of GISTs.^{3,6}

Complete gross surgical resection is the main treatment modality for GISTs. Until the advent of imatinib, there was no effective treatment for unresectable or metastatic GISTs. Imatinib is a well-tolerated agent that can inhibit the disrupted tyrosine kinase signalling pathways in GIST. Therapy with imatinib can induce objective responses and stabilisation of disease and can provide clinical benefit in the majority of GIST patients treated with the drug. It is important that imatinib is continued, because the disease will progress if the drug is stopped. The most common side effects seen in patients continuing on therapy have been periorbital oedema, peripheral oedema, fatigue, skin rash, myelosuppression and nausea/vomiting.^{3,6,7} Resistance to imatinib may occur in some patients caused by mutations in the targeted oncogene. Further investigations are necessary to identify drugs that override or reduce this refractoriness to imatinib.

REFERENCES

1. Cerny T, Gillessen S. Advances in the treatment of Non-Hodgkin's Lymphoma. *Ann Oncol* 2002;13(suppl 4):211-6.
2. Joensuu H, Fletcher C, Dimitryevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. *Lancet Oncol* 2002;3:655-64.
3. Singer S, Rubin BP, Lux ML, et al. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol* 2002;20:3898-905.
4. Gelderblom H, Hogedoorn PCW, van der Graaf WTA, Verweij J. Imatinib, een specifieke tyrosinekinaseremmer, voor de behandeling van patiënten met een gastro-intestinale stromaceltumor. *Ned Tijdschr Geneesk* 2003;147(42):2051-5.
5. Heinrich MC, Blanke CD, Druker BJ, Corless CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. *J Clin Oncol* 2002;20:1692-703.
6. Judson I. Gastrointestinal stromal tumours (GIST): biology and treatment. *Ann Oncol* 2002;13(suppl 4):287-9.
7. Demetri GD. Targeting the molecular pathophysiology of gastrointestinal stromal tumors with imatinib. Mechanisms, successes and challenges to rational drug development. *Hematol Oncol Clin North Am* 2002;16:1115-24.