CASE REPORT

Neurofibromatosis and Atypical Presentation of Tumours

AC Beharry[1], C QuanSoon[2]

ABSTRACT

Type 1 neurofibromatosis (NF1) is a common genetic disease that increases a patient's lifetime risk for malignancy. Multiple myeloma (MM) is one malignancy that is associated with the disease less frequently and like other tumours, may be more aggressive as well as have unusual presentations. Therefore, MM must be considered as a differential diagnosis in any NF1 patient presenting with an extremity tumour. The aggressive nature can be assessed with haemoglobin concentration and specific tumour markers. The poor prognostic features of tumours in NF1 patients are often present and should be looked for in assessing this cohort.

Keywords: Malignancy, multiple myeloma, neurofibromatosis

INTRODUCTION

Type I neurofibromatosis (NF1) is an autosomal dominant disease, characterized by benign neurofibromas (1). The disease is common with an incidence of 1:2000 worldwide and 1:1141 in the Caribbean (2–4). Furthermore, there are over 1000 mutations associated with NF1 with the most common transformation to chromosome 17 (5, 6). As a consequence of these mutations, this subgroup of patients has a 2.7- to 5.0-times higher risk of cancer than the general population (7, 8). In addition, these tumours exhibit more aggressive behaviour and may have unique presentations (9).

Malignant tumours typically associated with NF1 tend to affect the nervous and gastrointestinal systems, such as peripheral nerve sheath tumours and gastrointestinal stromal tumours, respectively (9–11). Conversely, multiple myeloma (MM) is one malignancy that has rarely been associated with NF1 with little information available on the association between these two diseases (12–14). The case below will consequently illustrate a unique presentation of MM in a patient with NF1, highlighting the need for clinicians to be aware of rare disease associations in this population.

CASE REPORT

A 47-year-old female who presented with a three-month history of pain and swelling of her right shoulder, after an initial fall. She was diagnosed as a child with type 1 neurofibromatosis (NF1) with multiple plexiform neurofibromas and had a first-degree relative with the disease. For the initial injury, the patient was diagnosed with a ligamentous injury and discharged with analgesia. The shoulder on second presentation had generalized swelling and tenderness. In addition, passive and active ranges of motion were markedly decreased and she had no distal neurovascular deficit. X-ray from the initial fall (Fig. 1) revealed a lytic lesion at the greater tuberosity. The image from presentation (Fig. 2) showed lytic destruction of the metaphysis extending into the diaphysis. Additionally, periosteal calcification was noted, and the lesion was fractured with < 10° of the fracture.

The provisional diagnosis was a pathological fracture, secondary to a bone malignancy. Full clinical examination did not reveal any site for a potential primary lesion. Staging computerized tomography (CT) showed pulmonary lesions that could be a potential malignancy. The admission laboratory findings revealed a normocytic anaemia (Table). The immunoglobulin G (IgG), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were mildly elevated and were not meeting the criteria for diagnosis of multiple myeloma (MM). A tru-cut needle biopsy was performed with a 22G × 200 mm and showed histological findings consistent with a plasmacytoma fulfilling a major

From: [1]Department of Surgery, Port of Spain General Hospital, Port of Spain, Trinidad and [2]Department of Surgery, University of the West Indies, St Augustine, Trinidad.

Correspondence: Dr A Beharry, Department of Surgery, Port of Spain General Hospital, Port of Spain, Trinidad.
Email: allan_beharry@hotmail.com

 DOI: 10.7727/wimj.2017.159

criterion for MM. Immunohistochemistry was positive for CD138 and CD20, confirming the diagnosis and Ki-67 was > 80%, suggesting a high mitotic rate. Bone marrow aspirate performed revealed a > 30% plasmacytosis. The diagnosis of MM was made with two major criteria and a minor criterion (the lytic lesion of Fig. 1) being fulfilled. The patient started on a chemotherapy regime and is presently having her fracture managed conservatively.

Table: Showing the blood parameters to diagnose multiple myeloma

Blood parameter	Patient result	Normal range
Presenting haemoglobin concentration/g dL^{-1}	7.5	12.0–15.5
White blood cell count/ $\times 10^9$ L^{-1}	4.5	4.0–10.5
Mean corpuscular volume/fL	93.2	80–98
Platelet count/ $\times 10^9$ L^{-1}	185	140–400
Na concentration/m mol L^{-1}	133	135–145
K concentration/m mol L^{-1}	4.7	3.5–5.0
Ca concentration/mg dL^{-1}	9.3	8.0–10.0
Albumin concentration/g dL^{-1}	3.6	3.5–5.0
IgG concentration/mg dL^{-1}	2250	500–1500
IgA concentration/mg dL^{-1}	54.5	60–130
IgM concentration/mg dL^{-1}	26.5	50–150
B 2 microglobulin concentration/mg dL^{-1}	10	< 11.3

DISCUSSION

Type I neurofibromatosis (NF1) has many phenotypic variability with 1347 known mutations of which 20% are recurrent (15, 16). These mutations increase the incidence and severity of malignancies (17). In addition, multiple myeloma (MM) association with the condition is extremely rare with only three cases documented up to 2007 (12–14). The case, consequently, illustrated a patient with NF1 who had an aggressive case of MM, with a high mitotic rate. The case also highlighted the difficulty in diagnosing MM, with biopsies needed to make the diagnosis and the IgG levels were not meeting the criteria for diagnosing MM (18).

The presentation of a pathological fracture in NF1 patient requires working up the patient as a tumour of unknown origin, as opposed to assuming the lesion is neurological in origin. The clinical examination and computerized tomography (CT) did not reveal a primary source, highlighting the difficulty in diagnosing this subgroup. The presentation of upper limb fractures in MM patients is rare, however, with the presence of NF1 in the patient, atypical presentation of the disease should be expected (19).

The presence of aggressive tumours in NF1 patients is well documented. The case presentation showed only a three-month period from the presentation with a lytic lesion (Fig. 1) and gross bony destruction with a pathological fracture (Fig. 2). Furthermore, the patient was staged as Durie–Salmon staging III for MM, due to the low haemoglobin concentration, highlighting the rapid progression of the disease (20). The Ki-67 tumour marker of > 8% from immunohistochemistry confers decreased survival rates and is correlated to high proliferation (21). Consequently, the rapid progression of MM, high stage at presentation and presence of specific tumour markers confer poor prognosis to the patient, attributable to the presence of NF1 mutations.

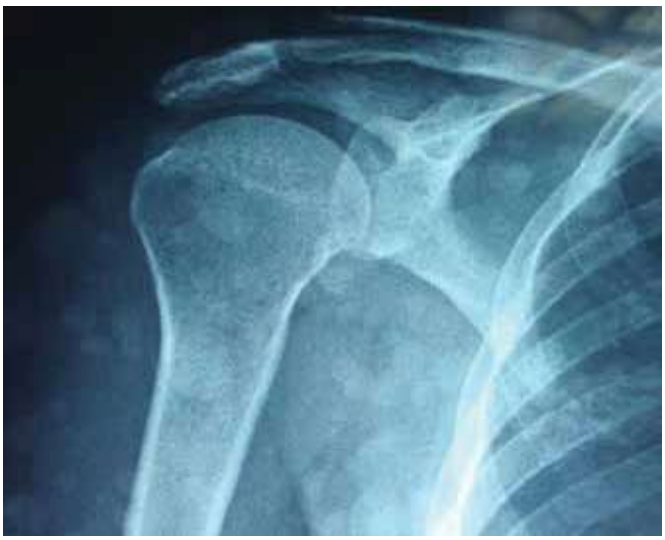

Fig. 1: Showing the lytic lesion (arrow) on initial presentation.

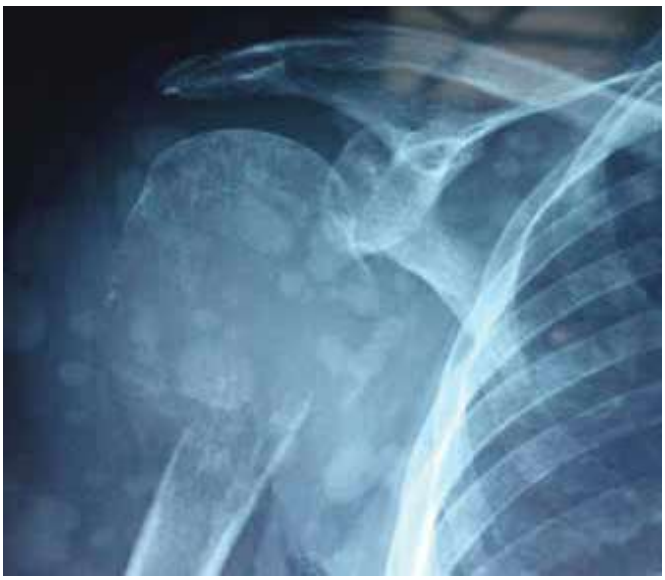

Fig. 2: Showing the pathological fracture at the proximal humerus.

NF1 is associated with malignancy that tends to be more aggressive. As illustrated by our case, disease progression in these patients can be rapid and atypical presentation is common. This knowledge of tumour behaviour in NF1 patients should allow early diagnosis and treatment, improving their survivorship.

REFERENCES

1. Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Lancet Neurol 2007; **6:** 340–51.
2. Huson SM, Compston DA, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. II. Guidelines for genetic counselling. J Med Genet 1989; **26:** 712–21.
3. Kehrer-Sawatzki H, Mautner VF, Cooper DN. Emerging genotype–phenotype relationships in patients with large NF1 deletions. Hum Genet 2017; **17:** 1–28.
4. Orraca M, Morejón G, Cabrera N, Menéndez R, Orraca O. Neurofibromatosis 1 prevalence in children aged 9-11 years, Pinar del Río Province, Cuba. MEDICC Rev 2014; **16:** 22–6.
5. Alkindy A, Chuzhanova N, Kini U, Cooper DN, Upadhyaya M. Genotype-phenotype associations in neurofibromatosis type 1 (NF1): an increased risk of tumor complications in patients with NF1 splice-site mutations? Hum Genomics 2012; **3:** 6– 12.
6. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet A 1999; **89:** 1–6.
7. Sørensen SA, Mulvihill JJ, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis. N Engl J Med 1986; **314:** 1010–5.
8. Zöller ME, Rembeck B, Odén A, Samuelsson M, Angervall L. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. Cancer 1997; **79:** 2125–31.
9. Walker L, Thompson D, Easton D, Ponder B, Ponder M, Frayling I et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. Br J Cancer 2006; **95:** 233–8.
10. Wallace MD, Pfefferle AD, Shen L, McNairn AJ, Cerami EG, Fallon BL et al. Comparative oncogenomics implicates the neurofibromin 1 gene (NF1) as a breast cancer driver. Genetics 2012; **192:** 385–96.
11. Maertens O, Prenen H, Debiec-Rychter M, Wozniak A, Sciot R, Pauwels P et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. Hum Mol Genet 2006; **15:** 1015–23.
12. Iagoda AV, Gasparian NV, Belotserkovskaia MI, Pavlova IB. A case of generalized plasmocytoma in a patient with Recklinghausen's neurofibromatosis. Klin Med 1995; **74:** 66–7.
13. Gregory R, Hill J. von Recklinghausen neurofibromatosis and myelomatosis. Br J Clin Pract 1990; **44:** 725–6.
14. Maharaj A, Singh VR, Lalchan SA. Lisch and the importance of his nodules. West Indian Med J 2014; **63:** 799–802.
15. Njei B, Sanchez H. Neurofibromatosis type 1, recurrent pulmonary embolism, and a periampullary carcinoid tumor: is there a link? Conn Med 2013; **77:** 77–80.
16. Ferner RE, Thomas M, Mercer G, Williams V, Leschziner GD, Afridi SK et al. Evaluation of quality of life in adults with neurofibromatosis 1 (NF1) using the Impact of NF1 on Quality Of Life (INF1-QOL) questionnaire. Health Qual Life Outcomes 2017; **15:** 34.
17. Kyle RA, Child JA, Anderson K, Barlogie B, Bataille R, Bensinger W et al. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003; **121:** 749–57.
18. Fairfield H, Falank C, Avery L, Reagan MR. Multiple myeloma in the marrow: pathogenesis and treatments. Ann NY Acad Sci 2016; **1364:** 32–51.
19. Durie BG, Salmon SE. A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975; **36:** 842–54.
20. Alexandrakis MG, Passam FH, Kyriakou DS, Dambaki K, Niniraki M, Stathopoulos E. Ki-67 proliferation index: correlation with prognostic parameters and outcome in multiple myeloma. Am J Clin Oncol 2004; **27:** 8–13.