

FDG-PET detection of primary bone marrow large B-cell lymphoma in a patient with hairy cell leukemia

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Abstract

We describe a case of hairy cell leukaemia (HCL) coexistent with non-Hodgkin's lymphoma (NHD). This combination is reported to be extremely rare with no clear demonstration of the clonal relationship between the two conditions. After a previous failure of purine analogue therapy, our patient was successfully treated with rituximab resulting in normalisation of blood cell count cessation of blood transfusion and negative iliac crest biopsy. Unfortunately, the patient developed intense and persistent bone pain during the 1st line treatment for HCL. Skeletal X-rays, neck-thorax-abdomen CT scan and repeated bone MRI were unremarkable and bone scintigraphy showed non-specific changes. Laboratory examinations were normal. To better evaluate bone scintigraphy results, we finally per-

formed FDG-PET/CT, which showed multiple foci of intense abnormal radiotracer uptake involving the bone marrow. An FDG-PET/CT guided bone marrow biopsy showed primary bone marrow diffuse large B-cell lymphoma (LBCL). Despite 2nd and 3rd line treatment, the patient died shortly after for central nervous system involvement by NHD.

The role of FDG-PET/CT in identifying bone and bone marrow localization of NHD is reviewed and an earlier use is suggested in poorly understood bone pain.

Key words: FDG-PET/CT imaging, lymphoma, bone marrow involvement, HCL

Case report

A 42-years-old woman with severe pancytopenia was referred for opinion in November 2002. She was suffering with thalassaemic trait and had been treated for ovarian adenocarcinoma with surgery and chemotherapy 13 years earlier. A mild splenomegaly was clinically detected in the absence of lymphadenopathy. Her blood picture showed WBC 1300/ μ L, neutrophils 650/ μ L, lymphocytes 550/ μ L; Hb 5.7 g/dL, MCV 76 μ m³ and platelets 89.000/ μ L. There was biochemical evidence of severe hypogammaglobulinemia (480 mg/dL) and elevated plasma β_2 -Microglobulin (β_2 -M) levels (3.5 mg/L). Renal and hepatic functions, erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH), and coagulation tests were normal and Coombs test was negative. Myelocentesis resulted in a dry tap while bone marrow biopsy showed a 80% substitution of normal cellularity by both diffuse and nodular infiltrate of small and medium sized B lymphocytes with oval or convoluted nuclei and large clear cytoplasm, a low proliferative index (Ki 67 = 2%) and an immunophenotypic pattern consistent with hairy cell leukaemia (HCL): CD20+, TRAP+, DBA44+, CD5–, CD3–. No hairy cells were detectable either in the peripheral blood smear, or by peripheral immunophenotyping. Standard chest X-ray and ultrasonography of the abdomen were normal.

The patient was treated firstly with pentostatin, then with cladribin, but blood transfusion remained necessary. Moreover, in February 2003, during the fifth course of pentostatin, she began com-

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plianing of lumbar pain radiating to the right pelvis/upper thigh. Abdominal and chest-computed tomographic (CT) scans, X-ray and repeated magnetic resonance imaging (MRI) of the dorso-lumbar spine and pelvis showed no abnormal features. A second bone marrow biopsy showed the persistence of a 30% lymphoid nodular and interstitial infiltrate with the identical morpho- and immunophenotypic features.

Her treatment was changed to rituximab with rapid and full haematological response, but only moderate pain relief. In September 2003, following six doses, her blood counts showed WBC 6830/ μ L, neutrophils 4600/ μ L, lymphocytes 1500/ μ L, Hb 13.2 g/dL, platelets 148.000/ μ L and β_2 -M plasma level 2.1 mg/L. In October 2003 a bone marrow biopsy demonstrated post-chemotherapeutic alterations in the absence of disease localization. Blood count, ESR and LDH were normal. Nevertheless, the patient continued to complain of increasing pain. Again, skeletal X-ray, CT scan and MRI were repeated, with negative results. In contrast, a total body bone scintigraphy finally showed increased radiotracer accumulation in the right coxo-femoral and ischio-pubic region, upper left femoral diaphysis, eyesockets, knees, shoulders and the sacro-iliac region symmetrically.

To better evaluate these non-specific findings, a 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT was performed in April 2004 (Figure 1) followed by a guided bone

marrow biopsy of the left femoral diaphysis. This demonstrated an aggressive high grade lymphoma, characterized by immunoblasts and polymorphous centroblasts in a diffuse pattern, expressing CD20, CD79a, CD10, Ig k for a 30%, nuclear and cytoplasmic bcl-6 antigen, a high proliferative index (Mib-1 > 90%), and ALK negative. These parameters, along with the absence of a low-grade component, were consistent with the diagnosis of primary bone marrow diffuse large B-cell lymphoma (LBCL). A blind iliac crest biopsy was negative for any disease localization. Shortly afterwards, LDH rapidly increased to 3780 U/L and Hb levels decreased to 9 g/dL; ESR was 120 mm, ferritin was 2857 ng/mL, fibrinogen 1000 mg/dL, β_2 -M 6 mg/L. An attempt was made to assess and compare B cell clonality of both disorders using a seminested PCR approach, as previously described [1]; unfortunately no major IgH gene rearrangements could be detected in both disorders with the primer pairs used for the assay (data not shown).

In May 2004 the patient was started on weekly chemotherapy scheme (VACOP-B). Diffuse bone pain rapidly resolved and Hb concentration, ESR, β_2 -M and LDH normalized. Unfortunately in July, six weeks after chemotherapy, she became sleepy and developed loss of memory, and central nervous system involvement with LBCL was confirmed with CSF cytology and immunophenotyping. Brain MRI showed diffuse subependymal disease. There-

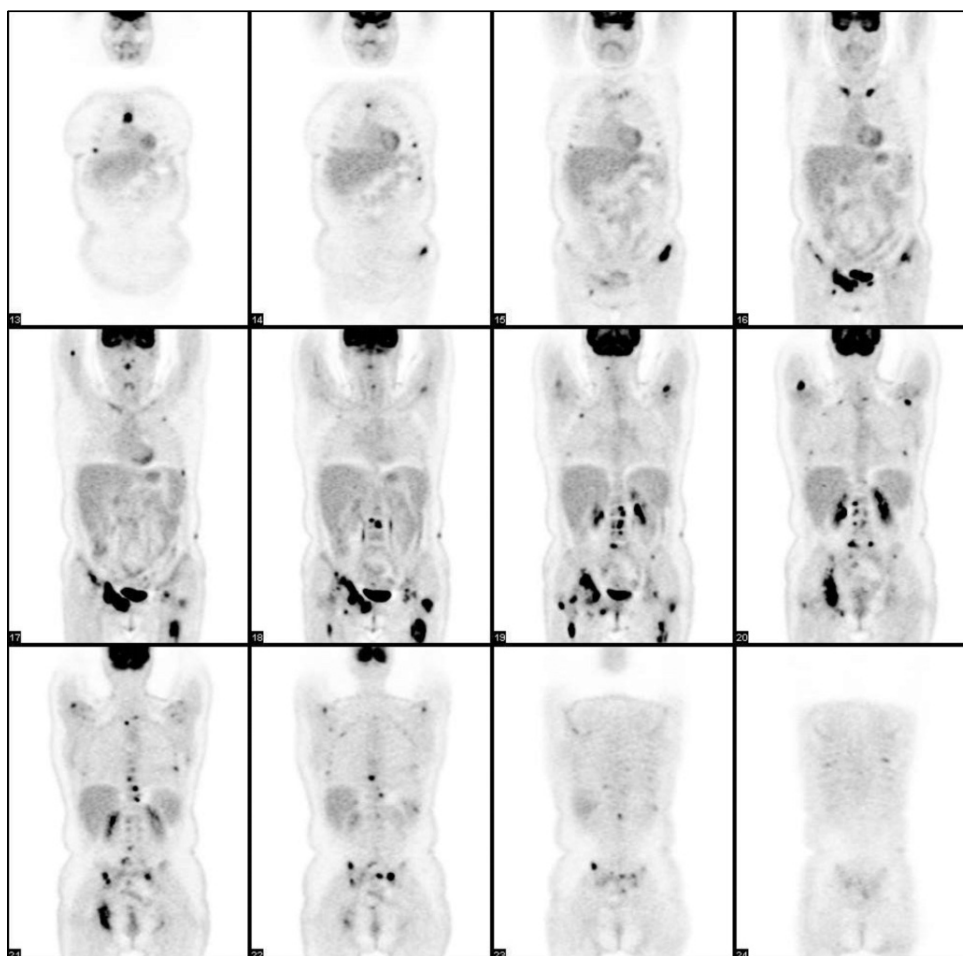


Figure 1. Coronal sections of FDG-PET/CT showing multiple foci of intense abnormal radiotracer uptake involving the bone marrow.

fore, the patient was given both intrathecal and systemic 3rd line chemotherapy with progressive neurological improvement. However, her clinical condition showed rapid deterioration culminating in cessation of chemotherapy. The patient eventually died of progression of her disease in August 2004.

Discussion

We have described a case of HCL in whom a diagnosis of coexisting primary bone marrow LBCL was finally confirmed with an FDG-PET/CT guided bone marrow biopsy. The coexistence of HCL with high-grade non-Hodgkin's lymphoma (NHD) is an exceptional event, and the clonal relationship between the two disorders was mostly inconclusive in the few reported cases [1], as is in our case. Moreover, in such cases, the diagnosis of high grade NHL would have easily been achieved by lymph node biopsy, had there been lymphadenopathy during the follow-up of HCL.

Our patient began suffering of intense bone pain during treatment for HCL. She was resistant to purine analogue therapy while rituximab therapy was followed by normalization of peripheral blood cell count, with only a mild relief of bone pain. Skeletal X-rays, neck-thorax-abdomen CT scan and repeated bone MRI were unremarkable, while bone scintigraphy showed non-specific findings only. Overall, her blood count values, ESR and LDH were normal, and blind iliac crest biopsy was negative. To better evaluate bone scintigraphy results, we performed FDG/PET-CT. At present, the role of FDG-PET/CT in the staging of Hodgkin's disease (HD) and aggressive NHD seems well established [2, 3] but low or absent FDG uptake may limit the use of FDG-PET in indolent lymphomas [2–4]. Moreover, several reports have suggested that bone marrow involvement by lymphoma can be accurately imaged by FDG-PET scanning at least in aggressive subtypes [2, 3, 5]. However, a recent retrospective study have shown that FDG-PET failed to detect a bone marrow involvement with a positive iliac crest biopsy in 4 out of 32 LBCL cases [6]. No data are available of whether HCL is detectable in bone marrow or spleen by FDG-PET. However, isolated reports indicate that FDG-PET may be valuable for the detection of localized relapse of acute leukaemia in bone marrow and extramedullary sites [7, 8].

It is well established that FDG-PET/CT is more sensitive and specific than bone scintigraphy in the detection of lymphomatous bone infiltration [9]. MRI seems to be superior to radio-colloid imaging in this setting [10], but its feasibility is limited to regional marrow assessment and unfortunately in our patient repeated MRI did not help to clarify the diagnosis. Furthermore, FDG-PET/CT has been shown to be more sensitive than biopsy, revealing focal lesions which can be easily missed by blind iliac crest sampling [1] which is appreciated since sampling error of patchy disease

are known to occur in between 30–50% of aggressive NHD and HD patients [11, 12]. It has been suggested that normal marrow appearance with FDG implies normal marrow histology in patients with accumulation in lymph nodes. Conversely, confirmatory marrow biopsies should be performed in all patients with abnormal marrow FDG uptake, using the PET scan to select the site of the biopsy [2, 3]. In our patient the diagnostic role of FDG-PET imaging in revealing bone and bone marrow involvement by LBCL has been fundamental, suggesting that FDG-PET may have a place early on, in the exploration of poorly understood bone pain.

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