Case Report

Aplastic anemia evolving to myelodysplastic syndrome and later to a lymphoproliferative malignancy in a treated case of carcinoma breast: A case report emphasizing the importance of PET-CT in cutaneous T cell lymphoma

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ABSTRACT

Although aplastic anemia (AA) and myelodysplastic syndrome (MDS) are separate entities with different management, distinction between the two can be difficult on morphological basis due to hypocellularity of bone marrow. MDS is one of the serious complications of AA. Karyotyping is definitive in the diagnosis of MDS. Better and robust investigations like ^{18}F-Fluoro-deoxy-Glucose Positron Emission Tomography/Computed Tomography (^{18}F-FDG PET-CT) are essential in high risk patients with haematological malignancies and in those relapsing within a short period of time after initiation of therapy or having refractory disease. It might be helpful in the development of individual treatment algorithms for these high-risk patients. There may be unique problems in hematological malignancies where the transformation of one pathology into another may be silent with no biomarkers that can predict this transformation e.g. transformation of MDS from AA. Studies have shown that immune suppression can lead to a variety of haematological and lymphoproliferative disorders which may co-exist. ^{18}F-FDG PET-CT may be useful in identifying the primary or occult sites of malignancy and also can direct the site from which biopsy can be attempted. We present a patient with Carcinoma right breast who developed hematological and lymphoproliferative disorders during the course of her treatment. In this case, AA transformed to MDS with abnormal karyotype (chromosome 9 mutation) and then progressed further to manifest cutaneous T cell lymphoma before patient succumbed to her illness. Immune mediated suppression of haemopoiesis has been considered the most important mechanism in this case.

Key words: Aplastic anemia; Myelodysplastic syndrome; Cyclosporine; Carcinoma breast; Methotrexate; Cutaneous T cell lymphoma

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INTRODUCTION

Leukemias, lymphomas and other hematological malignancies represent different manifestations of generalized insults to the bone marrow. A primary insult to the bone marrow could simultaneously lead to several abnormal haemopoietic cell clones, while one dominating and the other present but below the level of detection [1].

Aplastic anemia (AA) is a disease of bone marrow and is characterized by presence of pancytopenia in the peripheral blood and a hypocellular marrow in which normal haemopoietic marrow is replaced by fat cells. On the other hand myelodysplastic syndrome (MDS) is a disorder of haemopoietic stem cell that is characterized by variable degree of trilineage dysplasia and cytopenias in the background of a normal or hypercellular marrow reflecting ineffective haemopoiesis. AA are considered to be a better entity rather than MDS as blood picture is usually characteristic [1]. Bone marrow morphology is also unambiguous, and the response to therapy is relatively predictable in AA rather than in MDS. ^{18}F-FDG PET-CT has an important role in staging, therapy response and radiation planning in many cancers especially lymphomas. Structural imaging modalities require enlargement of anatomic structure to suggest tumor. The introduction of high-resolution CT and MRI improved the ability to identify these morphologic changes but could not reliably predict the clinical outcome after therapy. Changes in anatomic structures are slow and initially enlarged tumor sites may remain enlarged without tumor activity because of the development of fibrosis and/or tumor necrosis. Here we describe a known case of Carcinoma right breast who developed hematological and lymphoproliferative disorders during the course of her treatment. Cutaneous T cell lymphoma is an aggressive malignancy which is exemplified by ^{18}F-FDG PET-CT in this patient who presented with multiple cutaneous nodules. The exact site for biopsy and staging was highlighted by PET-CT imaging.

CASE HISTORY

64 years old lady with carcinoma right breast, post modified radical mastectomy and chemotherapy (Methotrexate, doxorubicin and 5 flurouracil) presented with excessive fatigue and easy bruising approximately 8 months post chemotherapy. Patient showed a high mean corpuscular volume and a severely hypocellular or almost empty marrow clinching the diagnosis of AA. Patient underwent immunosuppressive therapy with antithymocyte globulin (ATG) and cyclosporine A (CsA). After 2 years, patient presented with fever since one month off and on. Hematological investigations revealed a leucoerythroblastic blood picture with thrombocytopenia, atypical cells and dyspoiesis in RBCs and WBCs. Aberrant megakaryocytes, anisocytosis, microcytic hypochromic cells were seen. Patient also showed cabot ring and basophilic stippling. Leucopenia was noted and neutrophils showed hypogranulation and Pseudopelger Huet and atypical cells (Figure 1).

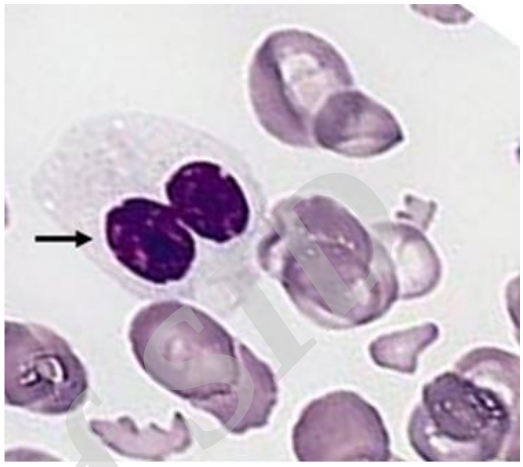

Fig 1. Hypogranular neutrophil with a pseudo–Pelger-Huët nucleus in our patient with MDS (arrow).

A diagnosis of MDS was entertained based on presence of megakaryocytes and associated karyotypic abnormalities (monosomy for chromosome 9). Megakaryocytes are the most reliable lineage to distinguish MDS from AA: small mononuclear or aberrant megakaryocytes are typical of MDS, whereas megakaryocytes are markedly reduced or absent in AA. Thus AA transforming to MDS was concluded. Once MDS sets in ATG therapies are futile and usually ineffective, so therapy in this patient was supportive with transfusion of blood products.

After 6 months, patient presented with rashes, fever and multiple skin nodules of 4mm size over anterior thorax, abdomen and limbs. Lactate dehydrogenase level was raised. Whole body ^{18}F-flurodeoxyglucose positron emission tomography /computed tomography (^{18}F-FDG PET-CT) scan was requested to look for lymphoma or sites of occult infection. Scan showed ^{18}F-FDG avid left axillary lymph nodal deposit (Figure 2) and multiple cutaneous ^{18}F-FDG avid nodules (Figure 3). There was abnormal increased ^{18}F-FDG uptake in bone marrow indicating a stimulated marrow (Figure 4). Skin biopsy and immunohistochemistry revealed T cell lymphoproliferative neoplasm with high Ki index. Patient was started on palliative chlorambucil and 6 – mercaptopurine. In view of progressive cutaneous lesions (nodules showing further increasing size and

extent), it was decided to change to 2nd line with high dose dexamethasone, vincristine and cyclophosphamide. Patient succumbed in a few weeks time.

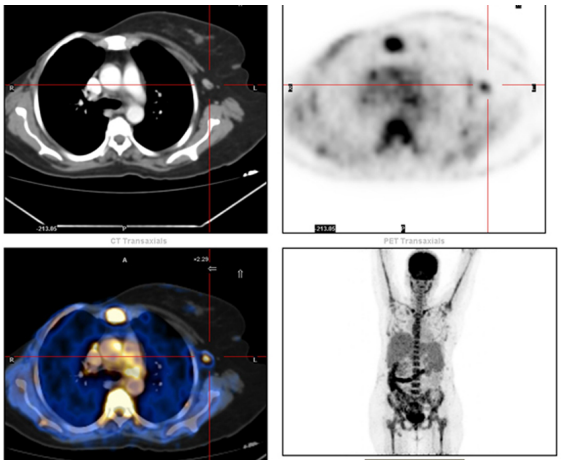

Fig 2. Whole body FDG PETCT transaxial images showing ^{18}F-FDG avid left axillary lymph nodes with an SUV (standard uptake value in gm/ml) of 3.0.

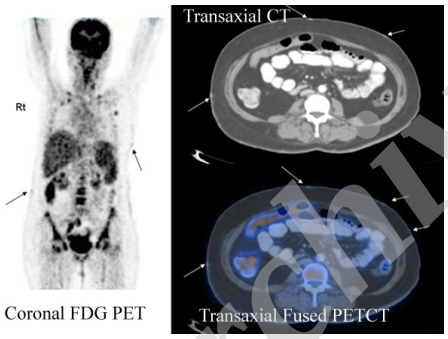

Fig 3. ^{18}F-FDG PETCT images show minimally increased FDG uptake in multiple enhancing thoracic and abdominal skin nodules (SUV Max 1.5). Splenomegaly present with no increased FDG uptake.

DISCUSSION

Aplastic anaemia is a rare haematological disorder which is thought to be immune mediated. It is characterized by T-cell mediated organ-specific destruction of bone marrow haematopoetic cells. As per International Agranulocytosis and Aplastic Anaemia Study in Europe, the incidence has been reported to be 2.0/million [1]. The incidence is 2 to 3 times higher in Asia than in Europe [2] Abnormal karyotype in MDS signifies a poor response to immunosuppressive therapy as in our case [3]. Both AA and MDS can be triggered by chemotherapy, radiotherapy, toxic chemicals and certain viral infections.

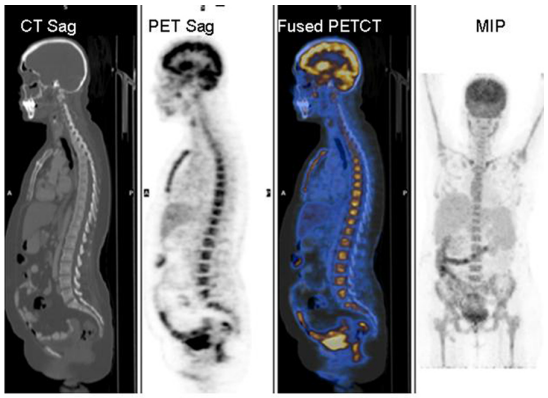

Fig 4. Sagittal section of ^{18}F-FDG PET-CT showing heterogenous increased ^{18}F-FDG uptake in bone marrow (SUV Max 6.7).

The link between immunosuppression and malignancy is clearly illustrated in literature as seen in patients with HIV and post renal transplantation [4]. These patients have an increased risk of lymphoma which is inversely correlated to CD4 counts [5].Similarly immunosuppressants and anticancer drugs are believed to bind lymphocytes, especially T lymphocytes, inhibiting calcineurin, which in turn leads to a downregulation of transcription of interleukin 2, IL-2. Other proposed mechanisms for enhanced tumor progression with immunosuppressive therapy, including direct and indirect cellular effects via the induction of tumour growth factor, TGF-β, angiogenesis stimulation by VEGF and through suppression of DNA repair and reduced p53-induced apoptosis. Our patient received CsA and anticancer drugs for breast malignancy which may have triggered an immune mediated new lymphomatous malignancy. Methotrexate, a common anticancer drug used in breast malignancy has been implicated in impairment of cellular immune control of tumor proliferation when compared to other cytotoxic agents [6].

Peripheral T cell lymphoma (PTCL) is a rare type of non-Hodgkin's lymphoma (NHL). A study conducted in South India by Burad et al showed that 17.4% of all NHLs constituted PTCL [7]. Cutaneous T-cell lymphoma (CTCL) is one of the common types encountered. It occurs predominantly in males in 5th or 6th decade of life. Most patients with CTCL experience only skin symptoms, without serious complications.

Studies have shown that clonal abnormalities exist in MDS and PTCL. We attribute the same as a relating and triggering factor in our patient to manifest as MDS and immune mediated malignancies over a period of time. Thangavelu et al [8] analysed ctogenetically the peripheral blood lymphocyte cultures from 19 patients with mycosis fungoides or Sézary syndrome, a form of T cell lymphoma. Clonal

abnormalities involving chromosomes 10 and 17 were observed in 5 cases, clonal abnormalities involving chromosome 2 in 4 cases, and clonal abnormalities involving chromosomes 4, 5, 6, 9, 13, 15, 19, and 20 in 3 cases.

^{18}F-FDG PET-CT is an established investigation in the staging and response assessment of all types of lymphoma. It has no role in the identification of aplastic anemia or MDS. In CTCL, various cutaneous lesions, from thin subtle plaques to thick tumors, can be identified and can be correlated with cutaneous examination. In patients' with subcutaneous lesions, the CT part of PET-CT can provide the depth or thickness of lesions. The patterns of varying ^{18}F-FDG uptake in enlarged lymph nodes found within an individual patient as well as among different patients may potentially distinguish reactive from malignant adenopathy. Additionally, lymph nodes that did not meet staging size criteria (e.g., were not > 1 cm) revealed increased metabolic activity and, therefore, can be targeted for subsequent monitoring or biopsy. In addition, PET-CT identifies visceral involvement in unsuspected lymphoma cases further upstaging the disease. High ^{18}F-FDG uptake of bone marrow on ^{18}F-FDG PET images could be due to lymphoproliferative disorder or treatment interventions (e.g. G-CSF) or less likely breast cancer metastases.

CONCLUSION

Cutaneous T cell lymphoma is an aggressive malignancy which is exemplified by ^{18}F-FDG PET-CT in this patient who presented with multiple cutaneous nodules. The exact site for biopsy and the fact that there was extensive metastases was highlighted by PET-CT imaging. In summary, PET-CT can provide physiologic and anatomic information on the wide diversity of lymph nodal, cutaneous, subcutaneous and visceral involvement in CTCL and, therefore, has great potential for improving the staging and monitoring of response to therapy. It also indicates the aggressive nature of the disease thereby serves as a good prognostic marker.

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