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Case Report
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A Rare Case Report of Synchronous Multiple Myeloma and Chronic Myeloid Leukemia, a Diagnostic and Therapeutic Dilemma

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Abbreviations

MM: Multiple Myeloma; CML: Chronic Myeloid Leukemia; TKI: Tyrosine Kinase Inhibitor; CNL: Chronic Neutrophilic Leukemia; PCR: Polymerase Chain Reaction; IMWG: International Myeloma Working Group; VGPR: Very Good Partial Response; PS: Peripheral Smear

Background

Chronic Myeloid Leukaemia (CML) is a clonal hematopoietic stem cell disorder. Multiple Myeloma (MM) represents a malignant proliferation of plasma cells derived from a single clone. The co-occurrence of two rare malignancies CML and MM in the same patient is an extremely rare incident. We report a case of a 54 year old female who was simultaneously detected with MM and CML. At the outset, only chemotherapy for multiple myeloma was started as bone marrow and peripheral smear were not suggestive of CML. Subsequently Dasatinib was started in view of left shift seen in peripheral smear. It was both a diagnostic dilemma due to the rarity of synchronicity of these two malignancies and a therapeutic dilemma of whether to start with Tyrosine Kinase Inhibitor (TKI) as both peripheral smear and bone marrow was normal.

Case Presentation

A 54-year-old female with no comorbidities, a known case of solitary plasmacytoma (with kappa restriction, CD 138 positive), previously treated in July 2020 with definitive radiation therapy to the left pubic ramus. She received a dose of 50 Gy in 25 fractions from 3.6.2020 to 6.7.2020. She was on three monthly follow up since then. At the time of diagnosis, a baseline PET scan revealed no evidence of disease elsewhere, with bone marrow aspiration and biopsy were normal. Also, cytogenetic analysis by conventional karyotype was normal. In the month of June, 2021, she presented with pain in the left pubic region of three months duration. PET CT was done to evaluate disease status. It revealed a 2.8 cm × 5.6 cm lesion involving left pubic ramus and anterior acetabulum (SUV 26.1) which was 12.1 at baseline before radiation therapy. There was a cortical discontinuity with a small extra Osseous soft tissue. There was also a mention of interval development of additional small metabolically active osteolytic lesions in anterior L1 and L4 vertebra which raised the suspicion of progression to multiple myeloma. Work up for multiple myeloma was done that included bone marrow aspiration and biopsy, Serum myeloma panel [Serum Protein Electrophoresis (SPEP), Serum Immunofixation (SIF) studies, Free Light Chain Assay (FLC), beta 2 microglobulin] and cytogenetics. Bone marrow showed 10% plasma cells with no immature cells in myeloid lineage. SPEP showed presence of M spike in gamma region (band value: 0.52 g/dl). SIF studies showed IgG band with kappa band. Total proteins were in the range of 8.6 (normal range 6.4 g/dL to 8.2 g/dL). Ig G level in serum was 17.4 g. Ratio of involved and uninvolved free light chains was 150 with involved kappa light chain being 465. Hence a diagnosis of Multiple myeloma was established. Routine cancer cytogenetic studies at our institute (i.e., culture of unstimulated bone marrow aspirate at 24 h and 48 h of incubation at room temperature) revealed two clones of cells- one with normal karyotype and one with t(9;22) i.e., 46,XX,t(9;22)(q34;q11.2)[15]/46,XX[10].

A complete blood count with peripheral smear was normal with no leukocytosis with left shift or thrombocytosis or any abnormal cells. She was started on a three drug regimen (proteasome inhibitor bortezomib, lenalidomide and Dexamethasone with bisphosphonates) as per our institutional protocol for a standard risk stage III Standard risk multiple myeloma after a thorough discussion about the treatment options including transplant. However, the family refused for transplant. At this point of time, BCR ABL mutation was being considered as a part of normal

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variant as marrow and peripheral smear were normal. Hence, we decided to serially monitor the peripheral smear of the patient and took a decision to not expose the patient to TKI then. She completed 4 cycles of VRD (bortezomib/lenalidomide/dexona) till 20.10.21 following which reassessment was done by serum myeloma panel which was suggestive of Very Good Partial Response (VGPR) as per International Myeloma Working Group (IMWG) criteria with an absent M spike, normalization of serum FLC ratio. It was decided to continue with the same chemotherapy regimen. Her peripheral smear was being serially monitored at each visit. At her visit during cycle 5-D22, her PS was suggestive of left shift with 1% blasts, 6% myelocytes, 7% metamyelocytes, 12% band forms. Now we started her on TKI (Dasatinib 100 mg once a day) after reviewing the drug interactions with other drugs being used for multiple myeloma.

Discussion

We report a case of synchronous hematological malignancies, multiple myeloma coexistent with CML. Though bone marrow was not suggestive of CML, the characteristic translocation t(9,22) was present in the cells. We further did cytogenetic analysis to rule out Philadelphia positivity as a constitutional abnormality by the PHA (Phytohemagglutinin) induced peripheral blood cell culture with 72 h incubation at room temperature, which showed all cells as normal karyotype, thereby proving the existence of the t(9;22) translocation in our reference case as clonal. Following the conventional karyotype report, hybrid transcript for BCR/ABL 1 was quantified by IS MMR RT PCR assay. The ratio of BCR-ABL 1/ABL 1 transcript as represented in IS scale was detected to be 5.931%. Genomic breakpoint observed was e 13a2 which corresponded to p210. Other cytogenetic abnormalities seen in multiple myeloma like IGH rearrangement, p53 del, del 13q were negative. Unfortunately on conventional cytogenetics or FISH analysis it is not possible to comment on the type of cells that are carrying specific genetic aberrations. Hence a dilemma might arise as whether they were myeloma cells or leukemic cells which were harboring BCR-ABL1 translocation. Plasma cell enrichment by cell sorting of CD-138 expressing cells in bone marrow or peripheral blood by immunomagnetic methods has been widely applied for targeted molecular cytogenetic analysis of multiple myeloma cases [1-3].

The Philadelphia chromosome was originally detected by workers in Philadelphia as an abnormally short G-group chromosome in analysis of bone marrow metaphases from CML patients [4]. It is the first genetic abnormality to be associated with a human cancer. Now it's understood through chromosome banding techniques that Philadelphia chromosome was the result of a balanced translocation between chromosomes 9 and 22, denoted t(9;22)(q34.1;q11.21), where the derivative chromosome 22 is significantly smaller. Chromosomal abnormalities can be germline (constitutional) or acquired. Germline abnormalities could be heritable or non-heritable. t(9;22) is as either non-heritable constitutional or acquired. The Philadelphia chromosome is present in hematopoietic cells from patients with CML but not in non hematopoietic cells, including bone marrow fibroblasts [5]. BCR-ABL fusion transcripts resulting from translocation t(9;22), are hallmarks of Philadelphia chromosome positive ph + leukemia patients. This translocation is detected in >90% patients with CML and ~20% patients with Acute lymphoblastic leukemia patients [6]. There are three common variants of BCR ABL 1, p210 BCR ABL 1: This is created by fusion of ABL 1 at a2 with a breakpoint in the major BCR region at either e13 or e14 to produce an el3a2 or e14a2 transcript that is translated into a 210 kD protein [7-10]. This variant is present in most of the CML patients. It is present in one third of the patients with ph positive B cell acute lymphoblastic leukemia. p190 BCR ABL 1: This is created by fusion of ABL 1 at a 2 with a breakpoint in the minor BCR region at e1 to produce an e1a2 transcript into a 190 kD protein. This variant is present in two thirds of those with Ph+ B ALL (80% of childhood and 50% of adult Ph positive B-ALL) and a minority of patients with CML p230 BCR ABL 1: This is created by fusion of ABL 1 at a2 with a breakpoint in the mu BCR region at e19 to produce an e19a2 transcript which is translated into a 230 kD protein. This variant is seen in some patients with chronic neutrophilic leukemia.

There are three hypothesis that have been thought of with regard to the presence of BCR ABL rearrangement in our case.

The first one that we considered initially was that this rearrangement is a part of a normal variant, the significance of which could be found out on regular follow-up of this patient. A study by Jew Win Kuan et al. was done in normal population in southern Sarawak by performing quantitative PCR for BCR ABL1 with ABL1 as an internal control on total white blood cells. In this they demonstrated that the BCR ABL1 fusion gene is expected to be present in approximately 0.5% to 1% of normal individuals in that area. The positive subject in this study had BCR ABL1 Fusion gene of 0.002320.0032%, which is equivalent to MR4.5. In our patient in discussion, the BCR ABL1 transcript was 5.931%.

Secondly, tumorigenesis after exposure to environmental carcinogens such as ionizing radiation and chlorinated solvents is a well-known phenomenon. A common insult to the bone marrow can cause irreparable DNA damage potentially leading to neoplasms of myeloid and lymphoid origin. This might partially explain as the patient had been exposed to radiation therapy for plasmacytoma one year back.

Thirdly, treatment of first malignancy with cytotoxic drugs or radiation can potentially lead to secondary malignant transformation. The role of melphalan and cyclophosphamide in developing secondary malignancies is well documented in literature. Various secondary malignancies in lenalidomide-treated patients have also been described. Nevertheless, this hypothesis cannot be extrapolated to our patient because the two diseases were simultaneously detected. In addition, chronic antigenic stimulation due to multiple etiological factors may be involved in the development of simultaneous myeloid and lymphoid neoplasms. Other factors such as genotypic polymorphism may also be involved.

The other possibility is de novo ph+ multiple myelomas, which is an extremely rare event.

Another possible theory is the presence of a common malignant pluripotent progenitor stem cell which can be transformed to both lymphoid and myeloid lines [11].

Also, it has been proposed that a more sustainable environment for the formation of secondary tumors is created due to the presence of myeloma cells. Studies have showed that multiple myeloma cells have pleiotropic proliferative and antiapoptotic properties [12,13].

At the outset we had hypothesized it to be a normal variant and decided to keep under close observation. However, subsequently we started TKI, in view of left shift in peripheral smear. Chronic Myeloid Leukemia (CML) is a clonal hematopoietic stem cell disorder. The annual incidence of CML is 1.5 cases per 100,000 individuals.

Multiple Myeloma (MM) represents a malignant proliferation of plasma cells derived from a single clone. The co-occurrence of two rare malignancies CML and MM in the same patient is an extremely rare incident, and simultaneous diagnosis of CML and MM is reported in only five cases in the literature. Multiple Myeloma (MM) has been reported in association with a variety of myeloproliferative disorders, including polycythemia vera, myelofibrosis, essential thrombocythemia and Chronic Neutrophilic Leukemia (CNL). However, the association with Chronic Myelogenous Leukemia (CML) has been rarely reported [14]. A retrospective study between year 2013 to 2017 was done by Rouslan Kotchetkov et al. [15], in which they identified 46 patients with synchronous hematological malignancies, out of which 50% were myeloid + lymphoid 43% lymphoid + lymphoid and 7% were identified to have myeloid + myeloid synchronous malignancies , however none of them was CML with MM [15].

There are few reported cases of multiple myeloma with a Philadelphia chromosome. One reported case is of a 61-year-old man showing BCR ABL positive bone marrow after autologous bone marrow transplantation for multiple myeloma. Anecdotal cases of patients of multiple myeloma who developed CML after treatment or occurrence of multiple myeloma in a known case of CML on follow up are reported in literature.

Conclusion

After reviewing the literature, it is possible that the coexistence of these two hematological disorders is multifactorial. The occurrence can't be attributed to one factor alone. No formal guidelines have been established regarding the use of antimyeloma therapy along with TKIs used in the treatment for CML. In our patient we used the combination of Dasatinib with VRD regimen with good response and minimal toxicity to the patient.

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