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Whole-Body Low Dose CT (WBLDCT) as initial imaging modality for newly diagnosed multiple myeloma patients: Experience from a tertiary care center in North India

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Abstract

Background: For decades, the main imaging modality to detect bony lesions in multiple myeloma was whole body skeletal survey. Subsequently, CT, MRI and PET CT came to forefront with better sensitivity and specificity as well as detection of extramedullary soft tissue disease. The disadvantage with CT was the high radiation dose required; hence, low dose CT protocols were developed and has become one of the investigations of choice along with PET CT and MRI to detect lytic lesions in multiple myeloma. We herein present Whole Body Low Dose CT (WBLDCT) findings in patients of plasma cell dyscrasia presenting at our institute.

Materials and methods: We retrospectively collected the data from Hospital information system (HIS) & Radiology department for patients of plasma cell dyscrasia from Jan 2022 to Sept 2023.

Results: The patients included were 73, out of which there were 58 cases of multiple myeloma, 10 cases of MGUS, 2 cases of smouldering myeloma, 1 case of non-secretory myeloma, 1 case of solitary plasmacytoma and 1 case of plasma cell leukaemia. There was presence of lytic lesions in 31 out of the 58 patients of multiple myeloma. The most commonly affected site was vertebra (31.5%) followed by sacrum and pelvis (26%), ribs and sternum (20.5%), skull (20.5%) and long bones (20.5%). In 13 patients (17.8%), lytic lesions were involving 3 or more sites. Patients with 3 or more lytic lesions had more incidence of hypercalcemia and anemia at presentation. However, there was no statistically significant correlation with R ISS staging.

Conclusion: Imaging plays a very important role in the initial diagnosis and surveillance of multiple myeloma patients. Although our study was limited by a small sample size, this is one the first studies describing low dose whole body CT in myeloma patients in Indian scenario.

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Introduction

Multiple myeloma is characterized by neoplastic proliferation of plasma cells, associated with excessive production of monoclonal immunoglobulin and evidence of end organ damage related to plasma cell neoplasm. Multiple myeloma accounts for 12-15% of all hematologic neoplasms and is the second most common type of hematologic malignancy [1]. In India, the incidence of myeloma is estimated to be 1/100,000 [1]. The diagnosis of multiple myeloma requires one of the CRAB (hypercalcemia, renal insufficiency, anemia, bone lesion) criteria, along with the presence of >= 10% clonal plasma cells. According to IMWG, one or more osteolytic lesion on skeletal radiograph, CT or PET CT is required to classify as bone lesion [3].

Bone disease affects approximately 90% of patients along the disease course and is considered to be the commonest disease related symptom [4]. Skeletal survey or whole-body X Ray has been used for decades to detect osteolytic lesions and pathologic fractures in myeloma patients. However, this technique has limited sensitivity and specificity. Subsequently, CT and MRI came to forefront with better sensitivity to detect bony lesions as well as extramedullary soft tissue disease. The disadvantage with CT was the requirement of high radiation dose [5]. Hence, whole body low dose CT protocols were developed and has become one of the investigations of choice along with MRI and PET CT as the imaging modality in multiple myeloma patients. However, in India, low dose CT is available only at a few centres. Hence, there is paucity of data regarding its use in Indian setting. We herein present Whole Body Low Dose CT (WBLDCT) findings in patients presenting with plasma cell dyscrasia at our institute.

Materials and methods

We retrospectively collected the data from Hospital Information System (HIS) & Radiology department for patients of plasma cell dyscrasia from Jan 2022 to Sept 2023.

We characterized the patients according to the type of plasma cell disorder as MGUS, smouldering myeloma, plasma cell myeloma, non-secretory myeloma, plasma cell leukaemia and solitary plasmacytoma. We analysed the baseline characteristics of patients along with CRAB features and myeloma panel including serum protein electrophoresis, serum immunofixation, kappa/lambda free light chain. Bone marrow examination and FISH was done to detect cytogenetic abnormalities. FISH panel included t(11;14), t(4;14), t(14;16), t(14;20), gain 1q, del 1p32 and TP53 mutation. Patients were risk stratified according to ISS and R ISS criteria set by IMWG. The number and sites of osteolytic lesions as well as the presence of any extramedullary soft tissue disease was detected by WBLDCT. We further analysed the patients having 3 or more lytic lesions with respect to high-risk disease.

Results

The patients included were 73, out of which there were 58 cases of multiple myeloma, 10 cases of MGUS, 2 cases of smouldering myeloma, 1 case of non-secretory myeloma, 1 case of solitary plasmacytoma and 1 case of plasma cell leukaemia. The median age was 58 years. The male: female ratio was 1.4:1. At presentation, 67.1% patients had anaemia, 42.5% patients had renal insufficiency and 9.6% patients had hypercalcemia. On serum immunofixation, the commonest type was IgG kappa (38.4%) followed by IgG lambda (30.1%). On FISH analysis, 63% patients did not have any cytogenetic abnormality. Gain1q was the commonest cytogenetic abnormality seen in 26% patients. 5 patients (6.8%) had double hit myeloma and 2 patients (2.7%) had triple hit myeloma. According to ISS staging, 7.5% patients belonged to ISS I, 14.9% patients belonged to ISS II and 77.6% patients belonged to ISS III. When staged according to R ISS, 6% patients were R ISS I, 59.7% patients were R ISS II and 34.3% patients were R ISS III.

Table 1: Baseline characteristics of entire cohort.

	No of cases (%)
Hypercalcemia	7 (9.6%)
Kidney injury	31 (42.5%)
Anemia	49 (67.1%)
Lytic lesions	
Skull	15 (20.5%)
Vertebra	23 (31.5%)
Ribs and sternum	15 (20.5%)
Sacrum and pelvis	19 (26%)
Long bone	15 (20.5%)
Lytic lesions more than 3	13 (17.8%)
Extramedullary disease	7 (9.6%)
Immunofixation	
IgG kappa	28 (38.4%)
IgG lambda	22 (30.1%)
IgA kappa	4 (5.5%)
IgA lambda	7 (9.6%)
Kappa light chain	7 (9.6%)
Lambda light chain	4 (5.5%)
R ISS Stage	
1	4 (6%)
2	40 (59.7%)
3	23 (34.3%)

Lytic lesions were detected in 31 out of the 58 patients of multiple myeloma. The most commonly affected site was vertebra (31.5%) followed by sacrum and pelvis (26%), ribs and sternum (20.5%), skull (20.5%) and long bones (20.5%). In 8 patients, bone lesions were the only CRAB feature present, which upgraded the diagnosis from SMM to multiple myeloma. Extramedullary disease was present in 7 patients (9.6%). (Table 1) shows the baseline characteristics of the study population.

We further analyzed the 13 patients (17.8%) who had lytic lesions at 3 or more sites. 15.4% of these patients had hypercalcemia at presentation. On the other hand, among the patients with <3 lytic lesions, only 8.3% had hypercalcemia. Hence, there was a trend of association of hypercalcemia with increased number of lesions but it was not statistically significant (p 0.6

by Fisher exact test). 84.6% patients with lytic lesions >=3 had anaemia at presentation while only 63.3% patients in the cohort with <3 lytic lesions had anaemia. Again, this association was not statistically significant (p 0.198 by Fisher exact test). There was no association with renal injury. On serum immunofixation, 7 of these patients were IgG kappa, 2 were kappa LC, 2 were lambda LC, 1 was IgA lambda and 1 was IgA kappa. 8 of these patients had no cytogenetic abnormality while 5 patients had gain1q on FISH panel. We did not detect any other cytogenetic abnormality in these patients. Out of these 13 patients, 11 patients (84.6%) belonged to ISS Stage III while 2 patients (15.4%) belonged to ISS Stage II. However, on R ISS staging, 4 patients (30.8%) belonged to R ISS Stage III while 9 patients (69.2%) belonged to R ISS Stage II. Hence, there was no correlation of extensive bony lesions with higher stage or high-risk disease.

Discussion

The incidence of multiple myeloma is reported to be lower in India as compared to Western countries. However, the median age at presentation is around a decade earlier in Indian patients (55 years in Indian population vs 65 years in Western population) [2]. In our study, the median age at presentation was 58 years, in concordance to previously reported Indian literature. The male: female ratio was 1.4:1. UK and US based studies have also shown a slight male preponderance (54%-58% males) [1,6]. A large study at AIIMS which included 1658 patients with plasma cell dyscrasias showed 82.7% multiple myeloma, 1.8% MGUS, 0.8% smouldering myeloma, 0.7% plasma cell leukaemia and 4.5% plasmacytoma. Rest of the patients had Waldenstrom macroglobulinemia, Amyloidosis and POEMS syndrome [2]. Among the 73 patients in our study, 79.5% had multiple myeloma, 13.7% had MGUS, 2.7% had smouldering myeloma, 1.4% had plasmacytoma, 1.4% had plasma cell leukaemia and 1.4% had non secretory myeloma.

According to WHO, 20-30% of patients present with renal injury and up to 10% of patients present with hypercalcemia [7]. Another American study on real world presentation of multiple myeloma in 2342 patients showed anaemia in 42.2% patients, renal injury in 10.7% patients and hypercalcemia in 9.9% patients [8]. According to an Indian study on 115 patients, anaemia was found in 83.5% of patients, renal injury in 18.2% of patients and hypercalcemia in 15.6% of patients [9]. In our study, 67% patients presented with anaemia and 9.6% patients presented with hypercalcemia, which is in concordance to previous Indian literature. However, we had 42.5% of patients presenting with renal injury, which is higher than reported literature. On serum IFE, the commonest monoclonal protein reported across literature is IgG (54-58%) [10,11]. IgG kappa subtype has been reported as the commonest [9]. We also found IgG kappa to be the commonest subtype (38.4%), followed by IgG lambda (30.1%) and light chain type (15.8%). Overall, high risk cytogenetics was seen in 30.1% of patients. The incidence of high-risk cytogenetics was similar to Western literature [10]. Gain 1q has been reported in 30-43% of patients, t(4;14) in 14-20% patients, t(14;16) in 2-10% patients and del 17p in 10% patients [2]. Our study also showed gain 1q as the commonest cytogenetic abnormality (26%). The other abnormalities detected were t(11;14), t(4;14) and t(14;16), each seen in 5.4% of patients. Only 1 patient had del 17p at baseline. We had 6.8% patients with double hit myeloma and 2.7% patients with triple hit myeloma. This incidence was lower as compared to an extensive Indian study on cytogenetics of myeloma, which reported 13.3% patients of double hit myeloma and 5% patients of triple hit myeloma [12].

In our study, 7.5% of patients had ISS stage I, 14.9% had ISS stage II and 77.6% had ISS stage III. We had a grossly higher incidence of ISS stage III when compared to previous publications. According to previous reports, ISS III was seen in 19%-40% of patients [8,10,13]. A report on Indian population too reported ISS stage III only in 31% patients [9]. According to R ISS staging, 6% patients had R ISS I, 59.7% had R ISS II and 34.3% had R ISS III. In the IMWG cohort which included 3060 patients, R ISS stage I was seen in 28%, R ISS stage II in 62% and R ISS stage III in 10% patients. Hence, we had a higher incidence of R ISS stage III in our study.

At baseline, almost 80% of patients present with osteolytic bone lesions [14]. During the disease course, up to 90% of patients develop bone disease [4]. Hence, detection of bone lesions becomes an integral part in the workup of multiple myeloma. A number of cytokines involving different pathways has been implicated in the molecular pathogenesis of bone lesions including RANKL/OPG, Wnt, IL-6, IL-7 and IL-3 [15].

Whole body X Ray has been used for decades and is referred to as the gold standard for detection of bony lesions. However, conventional skeletal survey has been associated with many disadvantages. X Ray can pick up lytic lesions only when 30-50% of mineral density is lost. Hence, early lytic lesions are often missed leading to limited sensitivity. Also, presence of overlying tissue might interfere with detection of lytic lesions. On the other hand, bowel loops might mimic bony lesions causing false positive results [16]. Hence, a search for better imaging techniques with higher sensitivity was initiated.

Whole body CT was introduced which could detect osteolytic lesions <5 mm, leading to better sensitivity. It could also identify areas with a higher risk of fractures as well as detect soft tissue disease. However, the only disadvantage was the high radiation dose required (around 35mSv) [17]. To overcome this drawback, low dose CT protocols were developed. Horger et al did the initial pioneering work with whole body low dose CT and published their work in 2005 [18]. They established certain additional advantages, apart from lower radiation dose, like usage of intrinsic contrast of bony to avoid use of IV contrast and rapid acquisition time of approximately 75 seconds. WBLDCT can also be used to guide biopsy and plan for surgical interventions [18].

Gleeson et al. compared WBLDCT with skeletal survey, using WBMRI as the gold standard, in 39 patients. They reported a significantly improved diagnostic accuracy of 89.7% with LDCT as compared to 69.2% with skeletal survey [19]. Princewill et al also evaluated LDCT versus skeletal survey in 51 patients and used PET CT as the index imaging for comparison. CT detected significantly more lesions (968) versus skeletal survey (248) [20].

Whole body MRI can detect marrow infiltration by tumor cells even before frank lytic lesions and hence has higher detection rates. Also, no exposure to radiation is an added advantage with MRI.16 However, there are certain drawbacks. MRI requires IV contrast and hence cannot be used in patients with renal insufficiency, which constitutes a sizeable population of myeloma patients. It requires a prolonged acquisition time and is contraindicated in patients with indwelling metal objects [21].

PET CT is being increasingly used for workup in myeloma patients as it has the added advantage of being able to identify active and inactive lesions. Thus, it also helps during follow up to detect persistent metabolically active lesions as a marker for

refractory disease [16]. The only disadvantage is false positive results due to inflammation, post-surgical changes and brown fat [22].

We detected lytic lesions in 31 out of the 58 patients (53.4%) of multiple myeloma. The commonest site was vertebra (31.5%) followed by sacrum and pelvis (26%), ribs and sternum (20.5%), skull (20.5%) and long bones (20.5%). Our results were in agreement with internationally reported literature stating the highest incidence of lytic lesions in spine [17,20]. Rest of the sites like ribs, skull, pelvis and long bones show almost similar rates of lytic lesions [17]. We identified 8 patients (10.9%) having lytic lesions as the only end organ damage. We were thus able to upgrade the diagnosis of these patients from SMM to multiple myeloma. According to a study by Abdallah et al assessing the progression of high risk SMM patients, the commonest myeloma defining event was bone disease, seen in 37% patients [23]. We found extramedullary soft tissue disease in 9.6% of patients. This incidence was similar to previous reports of 7-17% myeloma patients having extramedullary lesion at presentation [24].

We further investigated the patients having extensive bone disease with osteolytic lesions at 3 or more sites. We had 13 such patients having involvement at 3 or more sites. In these patients, we found an increased incidence of hypercalcemia and anaemia, however the associations were not statistically significant. The majority of these patients were of IgG kappa type followed by light chain myeloma. There was no significant correlation with immunofixation. Cytogenetics revealed only gain 1q in 38% of patients. We did not detect any other cytogenetic abnormalities in this subset of patients. We also did not find any significant association of ISS or R ISS staging in these patients. To the best of our knowledge, there are no previous studies evaluating the association of the extent of bone disease with the clinicopathologic characteristics of multiple myeloma.

Whole body low dose CT is being used only in limited centres in India. Apart from being as sensitive as MRI and PET CT, it also offers certain other practical advantages. It requires a much lower radiation dose than conventional CT and has a rapid acquisition time of approximately 75 seconds. Additionally, the cost of WBLDCT is less than MRI and PET CT. At our centre, it costs around 4000 rupees less than PET CT and 2000 rupees less than whole body MRI. In a developing country like India, cost constraint plays a major factor and hence, LDCT can be used as an economical imaging modality.

The drawback of our study was the lack of comparison of WBLDCT findings with other imaging modalities. We did not compare the detection of osteolytic lesions with skeletal survey, WBMRI or PET CT. Hence, we could not comment on the sensitivity of LDCT in the detection of bone lesions.

Conclusion

We report the use of whole-body low dose CT to detect osteolytic lesions as well as extramedullary disease at baseline in all newly diagnosed patients of plasma cell neoplasm. WBLDCT has been established as an effective imaging modality with comparable sensitivities to other modern imaging techniques like MRI and PET CT. Since LDCT is being used only in centres in India, this is one of the very few studies evaluating its use in Indian settings. We also evaluated the extent of bone disease according to the number of sites affected. However, we did not find any significant association with other end organ damage criteria or risk stratification. Nevertheless, WBLDCT is a sensitive, rapid and cost-effective imaging technique and can be used as an initial imaging modality at baseline in multiple myeloma patients.

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