Frequency of Smoldering Multiple Myeloma in Patients with Abnormal Bone Marrow Plasma Cells Infiltrates

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ABSTRACT

BACKGROUND: Smoldering multiple myeloma is believed to be a rare, asymptomatic plasma cell disorder, representing an intermediate bridge between monoclonal gammopathy of undetermined significance and multiple myeloma. Smoldering multiple myeloma attained focus due to high risk of progression, major advances in the diagnosis, prognosis, and management. It is assumed that greater significance on the basis of recent trials with early therapy can be potentially beneficial to patients.

OBJECTIVE: To determine frequency of smoldering multiple myeloma in patients, presenting with plasma cell dyscrasias in the study area.

MATERIALS & METHODS: All cases having abnormal bone marrow plasma cells infiltrates with relevant investigations were divided into three groups. Group (1) Plasma cell infiltrates of <10%, Group (2) Plasma cell infiltrates of >10% and without any complications. Group (3) Plasma cell infiltrates of >10% and with complications hypercalcemia, renal failure, anemia, lytic bone lesions (CRAB). Cases with reactive plasma cells having no predominant multi nucleurity and no cytoplasmic flaming/skirting were excluded from the study. Data was analyzed on SPSS (Version 17.0).

RESULTS: A total of 26 cases of abnormal bone marrow plasma cells infiltrates were studied in both sexes with male and female ratio of (3:1) out of which 3 cases (11.5%) were found to have smoldering multiple myeloma. All of the three cases were males. The age was ranging from 36 to 80 years. Twenty two (84.7%) cases were having multiple myeloma and one (3.8%) were having monoclonal gammopathy of undetermined significance.

CONCLUSION: High risk smoldering multiple myeloma may be given with trials of therapy, before it develops into Myeloma complication/myeloma defining entity (MDE). However low risk Smoldering Multiple Myeloma needs close observation/follow ups.

KEY WORDS: Smoldering Multiple Myeloma (SMM), Plasma Cells (PC), Hypercalcemia, Renal failure, Anemia, Lytic bone lesions (CRAB).

INTRODUCTION:
Plasma cell dyscrasias represent a group of pre-neoplastic/neoplastic disorders of the bone marrow plasma cells. The plasma cells forming a mass in the bone marrow or soft tissue is known as a plasmacytoma while in case of more than one lesions is known as multiple myeloma (MM). This is a proliferative disorder, resulting in accumulation of cancer cells which force the healthy blood cells to crowd out. Rather than produce helpful antibodies, the cancer cells produce abnormal proteins that can cause complications¹. Treatment for all plasma cells dyscrasia is not always necessary for people who are not experiencing any sign symptoms. Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell (PC) disorder. SMM is distinguished from monoclonal gamopathy of undetermined significance (MGUS) primarily for clinical reasons, because the risk of progression to malignancy in the first 5 years after diagnosis is different: 10% per year in SMM vs 1% per year in MGUS²—SMM is biologically heterogeneous; it is a clinically defined entity comprising a subset of patients with biological premalignancy (MGUS) and a subset with biological malignancy (MM) who have not yet developed hypercalcemia, renal failure, anemia, or lytic bone lesions (CRAB) and/or other myeloma-defining events (MDE)³. Thus, SMM includes patients who behave like those with MGUS (with a very low rate of progression), a subset of a group having a much higher BM plasma cells (High risk) than that specified for (MGUS) and those who develop clinical symptoms and end-organ damage within the first 2 years of diagnosis⁴. SMM has since been well characterized, and high-risk subsets of SMM are increasingly recognized as the optimal phase of MM evolution in which to test early treatment strategies⁵. It is unfortunate that at the current time, there is no single pathological or molecular feature that reliably can be used to distinguish SMM patients who have only clonal premalignant PCs from those who have clonal malignant myeloma cells⁶.
The disease definition of SMM was recently updated to exclude patients with bone marrow plasma cells (BMPCs) of =60%, serum involved/uninvolved free light chain (FLC) ratio of =100, and those with 2 or more focal lesions (typically indicating focal bone marrow abnormalities) on magnetic resonance imaging (MRI). Such patients have an approximately 40% per year risk of progression and are now considered to have MM. The purpose of the present study was to focus on frequencies of various plasma cell dysrasias, specially SMM, including high risk cases in the study area. This will help to diagnose high risk SMM patients and to intervene at appropriate time.

MATERIALS AND METHODS:
This was a retrospective study carried out in Saidu Medical College and teaching hospital over a period of six years (from December 2011 to December 2017). A total of twenty six (26) patients were selected having abnormal clonal plasma cells infiltrates in their bone marrow with abnormal laboratory investigations and radiological changes consistent with plasma dyscrasias. All those cases having SMM diagnosed by the presence of > 10% but less than 60% plasma cell infiltrate in bone marrow with <1 focal radiological lesions of >5mm or monoclonal proteins of >3.0gm/dl were included in the study. Patients having morphologically normal cells, i-e; reactive plasma cells with no predominant multi nucleury, no cytoplasmic flaming/skirting were excluded. Data was analyzed on SPSS (Version 17.0).

Complete blood count (CBC) with erythrocyte sedimentation rate (ESR), Serum Protein electrophoresis, X-ray Skull / Pelvis and bone marrow cytology were performed for all of the 26 patients. CBC was performed by Automated Hematology analyzer and cross checked with smear. ESR was performed on Westergren tube method. Protein Electrophoresis was done on Automated (Minicap Sebia France) analyzer following full protocol. Bone marrow aspirates were collected from posterior superior iliac spine, smears prepared and then stained with Giemsa and Perl's stain. The bone marrow smears were examined under the microscope for the presence of abnormal Plasma cells / infiltrates.

Patients were divided into three groups on the basis of bone marrow plasma cells infiltration, abnormal laboratory investigations and radiological skeletal survey.

Group (1): Patients with PC infiltration of <10% (MGUS)
Group (2): Patients with PC infiltration of >10% and without any symptoms/complications (SMM).
Group (3): Patients with PC infiltration of >10% with symptoms / complications (CRAB), (MM).

Base line studies scrutinized included complete blood count, serum creatinine, serum calcium, skeletal survey, serum protein electrophoresis and bone marrow examination. Specialized imaging such as MRI of the spine and pelvis or PET and or CT as per recommendation to exclude MM were examined.

RESULTS:
The data of twenty six (26) patients, was collected from laboratory investigations, radiological survey and bone marrow reports done as a part of work up of a variety of disorders. Out of twenty six (26) patients the male to female ratio was 3:1, with the age range of thirty six (36) to eighty (80) years. Out of these total newly diagnosed patients 3 (11.5%) were having SMM. All of the three cases were male. Twenty two (84.7%) cases were having multiple myeloma and one (3.8%) was having monoclonal gammopathy of undetermined significance.

Table 1: Age wise frequency distribution of male and female patients, suffered from plasma cell dyscrasias.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-40</td>
<td>2</td>
<td>--</td>
<td>2</td>
<td>07.69</td>
</tr>
<tr>
<td>41-50</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>23.07</td>
</tr>
<tr>
<td>51-60</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>19.23</td>
</tr>
<tr>
<td>61-70</td>
<td>8</td>
<td>2</td>
<td>10</td>
<td>38.46</td>
</tr>
<tr>
<td>71-80</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>11.54</td>
</tr>
</tbody>
</table>

Table 2: Frequency distribution of various plasma cells dyscrasias.

<table>
<thead>
<tr>
<th>Type of plasma cells dyscrasias</th>
<th>Number of occurrences</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>22</td>
<td>84.7</td>
</tr>
<tr>
<td>SMM</td>
<td>03</td>
<td>11.5</td>
</tr>
<tr>
<td>MGUS</td>
<td>01</td>
<td>03.8</td>
</tr>
</tbody>
</table>
DISCUSSION:
Smoldering multiple myeloma is a premalignant, early stage of multiple myeloma. Though progressive, but the rate of progression of disease varies. Early intervention is believed to be helpful to slow down the pace of progression of disease. High risk, asymptomatic smoldering multiple myeloma needs to be diagnosed before the complication appear. High risk SMM is diagnosed by the presence of > 10% but less than 60% plasma cell infiltrate in bone marrow with <1 focal radiological lesions of >5mm or monoclonal proteins of >3.0 gm/dl. High risk SMM have more than 80% chances of multiple myeloma within two years of span. It is therefore, recommended to offer these patients with anti-myeloma treatment in order to avoid major complication and improve the quality of life of the ailing individual.

The present study was focused on frequencies of various plasma cell dysrasias, specially SMM, including high risk cases in the study area. This will help to diagnose high risk SMM patients and to intervene at appropriate time. The frequency of various types of plasma cell dyscrasias in our population and age range of the patients has been reported in this study. The data compiled is in the age range of 36 to 80 years of both sexes with predominant males of about 77% of the total cases, who suffered from plasma cell dyscrasias.

Persons in the age range of 50-80 years are predominating. However, an alarming lower age group has also been noted i-e; 30.8% were in the age group, below fifty years. This is consistent with the findings of early age malignancies in northern parts of Khyber PakhtunKhwa (KP). This low age occurrence of plasma cell dyscrasia is relatively uncommon in developed world. More studies are required to search for possible reasons at younger age as well as to assess the causes of its comparatively more occurrence in this area.

SMM being an early stage (premalignant) of MM be diagnosed before any complication (CRAB) appears. Although SMM is an asymptomatic disease, pain was a consistent clinical presentation (100%) in this study the possible reason may be low vitamin D level in this part of the world. Other symptoms of fever, anaemia, IRF, fractures (CRAB) were consistent of symptomatic MM. The frequency of SMM in our study is 11.5%, which is consistent with study done by Raj Kumar et al and Ravindran A et al in United States. These three patient had a plasma infiltrate of >10% but <30%. One of these three were having positive monoclonal proteins (in the gamma region) of 3g/dl, showing high risk activity as compared to the other two cases where no detectable monoclonal proteins were found on protein electrophoresis. All the three patients were having no Bence John's (BJ) protein in urine. All the three patients with SMM were having negative radiological findings, i.e. lytic bone lesion. Mild anaemia (Haemoglobin ranging from 10.0 to 11.5 gm/dl) with raised ESR were persistent in all the three cases. ESR was 40, 55 and 80mm/first hour in the three patients.

The standard of care for asymptomatic SMM is observation. These patients needs close follow up indefinitely. Laboratory visits be repeated after 2-3 months, then every 6-12 months, if the SMM remains stable. A skeletal survey should be repeated when progression is suspected. Patients with >1 focal lesion on MRI are now defined as active MM. With high risk SMM is now diagnosed by the presence of bone marrow PC infiltrates of <60% with <1 focal radiological lesion of > 5 mm, determined by MRI or an abnormal SFLC ratio, these patients having >80% risk of progression to MM after 2 years of diagnosis of SMM. Because a symptomatic progression may present with serious complications, the recommendations are to offer these patients with anti-myeloma treatment. Such a treatment aims to avoid major complications and improve quality of life of MM patients. Issues that are currently and very eagerly evaluated in early intervention SMM clinical trials. Selected high risk SMM patients with multiple risk factors or evidence of progression can be considered for therapy. Earlier intervention studies comparing an imminent with a delayed treatment with oral melphalan and prednisone for SMM patients could never show any benefit in terms of response rate.

A recently reported randomized trial compared thalidomide plus zoledronate verses zoledronate alone in SMM patients, the response rate was 37% in the thalidomide arm whereas no response were seen in the zoledronate arm. Earlier trials of bisphosphonate treatment demonstrated the absence of any clear anti-tumor activity, whereas having a strong effect on the bone metabolism in terms of anabolic effects and with a significant reduction in the incidence of skeletal related.
events. Bisphosphonates are recommended for SMM patients, especially with osteoporosis. One high risk case of SMM, has been on treatment with Thalidomide for the last two years, showing no progression of the disease and is having mild drug toxicity. This is consistent in terms of prognosis but in contrast to the element of toxicity as mentioned in a study performed by Rajkumar SV, et al and two other studies. As we used single agent (Thalidomide) only in one patient, so more studies are required for assessment of response rate with combination therapies in the study area.

CONCLUSIONS:
The identification of SMM and ultra-high risk patients with potential progression and with the introduction of new therapeutic agents has led to the advances in the management of myeloma precursor disease. The regimens, currently tested consist of single-agent and multi agents’ treatment options. For low-risk SMM patients; the standard care remains observation until development of high risk SMM or symptomatic MM. In patients with signs of osteoporosis and in ultra-high-risk patients, treatment with bisphosphonates should be considered. In the future, prospective studies are critical to correctly identify individuals who would receive the utmost benefit from early interventions.

REFERENCES:
