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Primary Intraoral Granulocytic Sarcoma: A Case Report and Review of Literature

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Abstract

Granulocytic sarcoma (GS) is a rare extramedullary malignant tumor composed of immature granulocytes, including myeloblasts, promyelocytes, and myelocytes. In most cases, these are associated with persisting blood dyscrasias such as acute myeloid leukemia and chronic myeloid leukemia. To date, 32 cases of GS involving orofacial region have been reported in the English literature. Out of these, only a few presented without any systemic complications. This case reports an unusual occurrence of GS without any associated leukemia involving the mandible of a 29-year-old male patient. Hematoxylin and eosin–stained sections revealed the presence of numerous rounds to ovoid myeloblasts with a multilobated, vesicular nucleus and a prominent nucleolus. The cells stained positive for Cluster of Differentiation 68, lysozyme, and myeloperoxidase. He later underwent chemotherapy but succumbed in the interim period of chemotherapy. We hereby report a unique case of GS of mandible in an apparently healthy individual who deteriorated rapidly; an early and accurate diagnosis of which could have been life-saving.

Keywords
- granulocytic sarcoma
- mandible
- MPO
- chemotherapy

Introduction

Myeloid sarcoma (MS), or granulocytic sarcoma (GS), is an extramedullary tumor consisting of immature cells of granulocytic lineage.[1] It was named "chloroma" by King[2] in 1853 due to the green color of the gross tumor caused by the myeloperoxidase (MPO) enzyme in the immature myeloid cells. It is commonly seen in patients suffering from acute and chronic leukemia or other myeloproliferative disorders. It has an incidence of approximately two in one lakh individuals and can occur at any age.[3,4] Common locations include soft tissues, peritoneum, lymph nodes, genitourinary system, gastrointestinal system, bone, and central nervous system; however, any other site of the body can also be affected.[3,5,6]

Oral involvement by GS is very uncommon with only 32 cases described in the English literature and PubMed database without systemic involvement (►**Table 1**).[7] Majority of the cases present as localized soft tissue masses, although less frequently intraosseous presentation had also been reported.[8] The case reported here presented a diagnostic dilemma as it had clinical similarity with odontogenic pathologies and histopathologically mimicked round cell neoplasm. We hereby report a unique case of GS of mandible

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Table 1 Summary of reported cases of granulocytic sarcoma having gnathic presentations[7]

Author	Age/sex	Site	Stains/IHC
Brooks, 1974	8/M	Maxilla R. Nostril, right upper molars	HE
Conran, 1982	2/F	Mandible R 2 × 3 cm. Swelling of the right lower mandible	HE
Takagi, 1983	25/F	Gingiva L 4 × 1 cm. Swelling of the gingiva with pain	IHC—MPO
Reichart, 1984	35/F	Mandible R 1.5 × 1.5 cm. Brownish color tumor	Cytochemical staining—chloroacetate esterase
Castella, 1984	89/F	Hard palate L 2 × 1 cm. Exophytic, ulcerated gray–white lesion	Cytochemical staining—chloroacetate esterase
Rodriquez, 1990	56/M	Gingiva L 5 × 3 cm. Exophytic, reddish lesion with pain	IHC—lysozyme
Eisenberg, 1991	33/M	Multiple gingiva. Multiple, raised, granular-appearing, red nodules	Cytochemical staining—Sudan black, MPO
Menasce, 1999	63/F	Gingiva. NR	IHC—MPO
Tong, 2000	76/F	Gingiva R 4 cm in diameter. Diffuse, ulcerative, granular-appearing lesion	IHC—MPO, CD45
Lee, 2001	43/F	Gingiva L 3.5 × 1.5 cm. Exophytic, firm, black-pigmented lesion	IHC—MPO, CD68, Mac387
Jordon, 2002	62/F	Mandible apical. Periapical granuloma and chronic abscess	IHC—MPO, CD43, CD15
Antmen, 2003	12/F	Gingiva 4 × 3 cm. Bright red, soft, friable, edematous mass	IHC—MPO, lysozyme
Colella, 2005	62/F	Gingiva. Large swelling in the upper vestibular region	IHC—MPO, lysozyme, CD45
Koudstaal, 2006	36/M	Hard palate L 1 × 3.cm. Blue–gray, mucosa intact, normal texture	IHC—CD45, CD43, HLA-DR
Goteri, 2006	84/F	Hard palate R. Ulcerated, nodular, infiltrative mass	IHC—MPO, CD45, CD43, CD34
Yinjun, 2006	44/F	Gingiva R. Progressive enlargement mass with pain, ulcer	IHC—MPO, CD68
Lu, 2009	63/F	Gingiva R. Puce mass, surface graininess, easily bleeding	IHC—MPO, CD34, Bcl-2
Qiu, 2010	16/F	Condyle L. Preauricular swelling, restriction mouth open	IHC—MPO
Colović, 2011	55/F	Mandible L. Large mucosal tissue swelling	IHC—CD117, CD45, CD68, lysozyme
Guastafierro, 2013	56/F	Gingiva. Large swelling in the upper vestibular region	IHC—MPO, CD45, CD68, lysozyme
Mei, 2013	56/M	Maxilla L 4 cm in diameter. Soft and solid mass	IHC—CD34, CD45, CD56, CD117, MPO
Chaudhuri, 2013	60/M	Lip. Nontender, firm, lumpy swelling. Cytochemical staining—immature myeloid cells	
Sharma, 2014	9/M	Maxilla L 3 × 3 cm. Single ill-defined, diffuse swelling	IHC—CD31, MPO, vimentin, CD99
Ponnam, 2014	45/F	Gingiva L 5 × 5 cm. Lobulated, firm, nontender and erythematous growth	IHC—CD45, CD68, CD117, MPO
Moshref, 2014	45/M	Gingiva, palate. Red and soft with irregular surfaces	IHC—CD45, C-Kit
Wang, 2014	27/M	Buccal mucosa L 3 cm in diameter. Firm mass without tenderness	IHC—MPO, CD34, CD68, CD117

Table 1 (*Continued*)

Author	Age/sex	Site	Stains/IHC
Dinesh Kumar, 2016	62/F	Gingiva. Gingival enlargement without purulent discharge	IHC—MPO, CD43
Sengupta, 2016	2/M	Mandible L 4 × 2.5 cm. Firm to hard, circumscribed, mildly tender swelling	IHC—CD45, CD68, lysozyme
Aboelhassan, 2017	67/F	Hard palate R 4 × 5 cm. Red painless swelling	IHC—MPO, CD43, CD117
Kumar, 2017	28/M	Mandible L. Ill-defined bony hard swelling	IHC—CD45, MPO
Shen, 2018	41/F	Gingiva. Blue–gray discoloration gradually developed	IHC—MPO, CD68, CD117, Ki-67
Hu, 2020	49/F	Hard palate R 3 × 2 cm. Ulcerated surface mucosa	IHC—MPO, CD4, Bcl-2, CD117
Present case	29/M	Mandible L. Ill-defined swelling	IHC—CD 68, lysozyme, MPO, negative CD1a, S-100, leucocyte common antigen, CD20, and CD3. Ki-67—55%

Abbreviations: CD, Cluster of Differentiation; F, female; HE, histologic examination; IHC, immunohistochemistry; Ki-67, proliferative index 67; L, left; M, male; MPO, myeloperoxidase; NR, not recorded; R, right.

in an apparently healthy individual who deteriorated rapidly; an early and accurate diagnosis of which could have been life-saving.

Case Presentation

A 29-year-old male patient reported to oral pathology department with swelling in the extraction site of the lower left teeth region associated with numbness of the ipsilateral side of the lower lip for a few months. The swelling was initially small and has increased to its current size over 2 months (►**Fig. 1**). The patient also reported occasional fever, pain, and persistent weight loss. No history of external trauma was reported.

Extraorally, there was a diffuse swelling occupying the left lower one-third of the face, measuring about 3 cm × 3 cm in size and extending from the mental foramen anteriorly to the posterior angle of the mandible; superiorly, below the junction of the middle and lower third of the face, and inferiorly up to the lower border of the mandible. On palpation, the swelling was tender and slightly compressible in places.

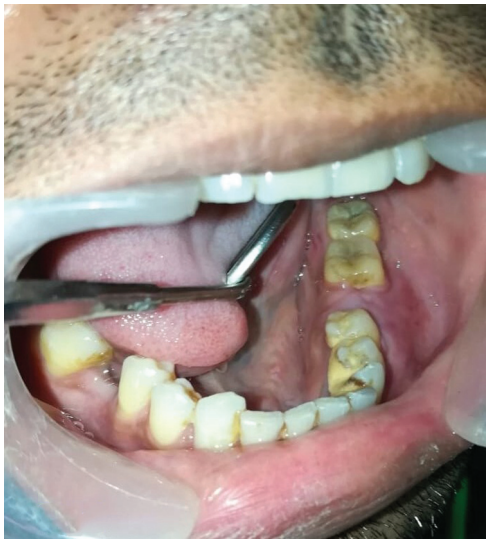

Fig. 1 A diffuse swelling, extending from permanent left mandibular first premolar to posterior left mandibular second molar with slight obliteration of buccal vestibule than the lingual.

Intraorally, an ill-defined, diffuse swelling in the edentulous alveolar ridge was noted which extended anteriorly from the permanent left mandibular first premolar to posteriorly left mandibular second molar with more obliteration of the buccal vestibule than the lingual vestibule. The overlying mucosa was slightly edematous and erythematous without ulceration.

In an older orthopantomogram (OPG), we noted that there was the presence of a mixed radiolucency and radiopacity with unequal widening of periodontal spaces with respect to tooth 36 and regional resorption of bone along the mesial root of tooth 36. But when he visited a local quack with pain and discomfort, tooth 36 was extracted. The persistence of symptoms made him visit our department where a repeat OPG was done. This new one revealed mixed radiolucency and radio-opacity with ill-defined border underneath the extraction socket (►**Fig. 2a**). There was also resorption along the mesial and certain areas of the distal aspect of tooth 35. Thereafter, cone beam computed tomography (CT) was advised for clarity which revealed a lytic lesion extending from tooth 33 to the left ramus of the mandible measuring about 3 cm × 2.5 cm × 2 cm (►**Fig. 2b–d**). Analyzing the image modalities and clinical data, the differential diagnoses considered were osteomyelitis, odontogenic tumor, or malignant lesion.

Routine hematological investigations were within normal limits (►**Table 2**).

He was then referred to oral and maxillofacial surgery for further evaluation. Ethics committee approval and written consent from the patient and their family were taken. Segmental hemimandibulectomy was performed and the composite specimen (measuring 5 cm × 1 cm × 2.5 cm) was

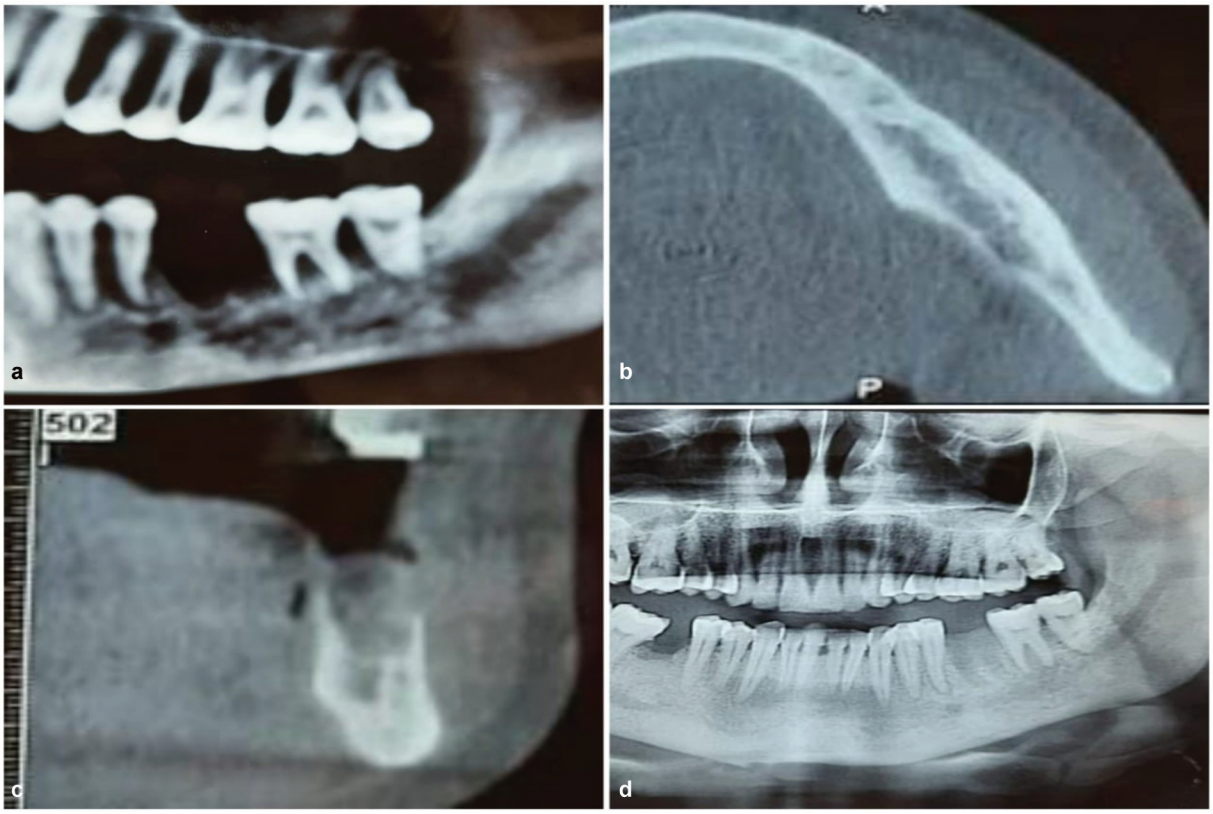

Fig. 2 (**a**) A mixed radiodensity underneath the extraction socket of tooth 36. (**b–d**) A lytic lesion extending from tooth 33 to the left ramus of the mandible measuring about 3 cm × 2.5 cm × 2 cm.

sent for histopathological evaluation along with the associated salivary gland.

Hematoxylin and eosin (H & E)-stained sections showed numerous rounds to ovoid cells mimicking myeloblasts having multilobated, vesicular nucleus, with a prominent nucleolus. The nucleus revealed pronounced hyperchromatism with an increased nuclear-to-cytoplasmic ratio. Most of the cells had finely dispersed nuclear chromatin and scattered mitotic figures. The cytoplasm of the neoplastic cells was mostly agranular showing varying degrees of basophilia. Few cells showed eosinophilic granulation (►**Fig. 3a**). Overall histopathological diagnosis was suggestive of malignant round cell neoplasm such as malignant lymphoma, MS, rhabdomyosarcoma, and poorly differentiated squamous cell carcinoma.

As there was considerable ambiguity regarding diagnosis, immunohistochemical (IHC) staining was performed which revealed cells to be Cluster of Differentiation (CD)68, lysozyme, MPO positive (►**Fig. 3b–d**) and negative for CD1a, S-100, leucocyte common antigen (LCA), CD20, and CD3. The proliferative index (Ki-67) was found to be 55%.

The overall IHC study was suggestive of GS. He was advised to consult a hemato-oncologist for necessary treatment. A positron emission tomography (PET)/CT was done which revealed no evidence of metabolically active disease or distant metastasis.

The patient has prescribed 10 courses of induction chemotherapy comprising injection daunorubicin hydrochloride 110 mg (days 1–3) and injection cytarabine 180 mg (days 1–7).

Table 2 Routine hematological investigations: all were within normal limits

Blood parameters	Values
Hb %	13 g%
ESR	42 mm (1st h)
BT	1 min 43 s
CT	4 min 5 s
PT	13.9
ApTT	31.6
INR	1.11
FBS	78 mg/dL
PPBS	87 mg/dL

Abbreviations: aPTT, activated partial thromboplastin time; BT, bleeding time; CT, clotting time; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; Hb, hemoglobin; INR, international normalized ratio; PT, prothrombin time; PPBS, postprandial blood sugar.

At that time, his routine hematologic assay revealed a drop in the hemoglobin count, thus a bone marrow examination was advised where moderate anisocytosis and normal to macrocytosis with mild hypochromia were observed. The striking feature was the presence of abundant round to oval cells with open-faced hyperchromatic nuclei similar to the neoplastic cells found in incisional biopsy specimen. Mitotic activity was also noted in the cells. Unfortunately, the patient

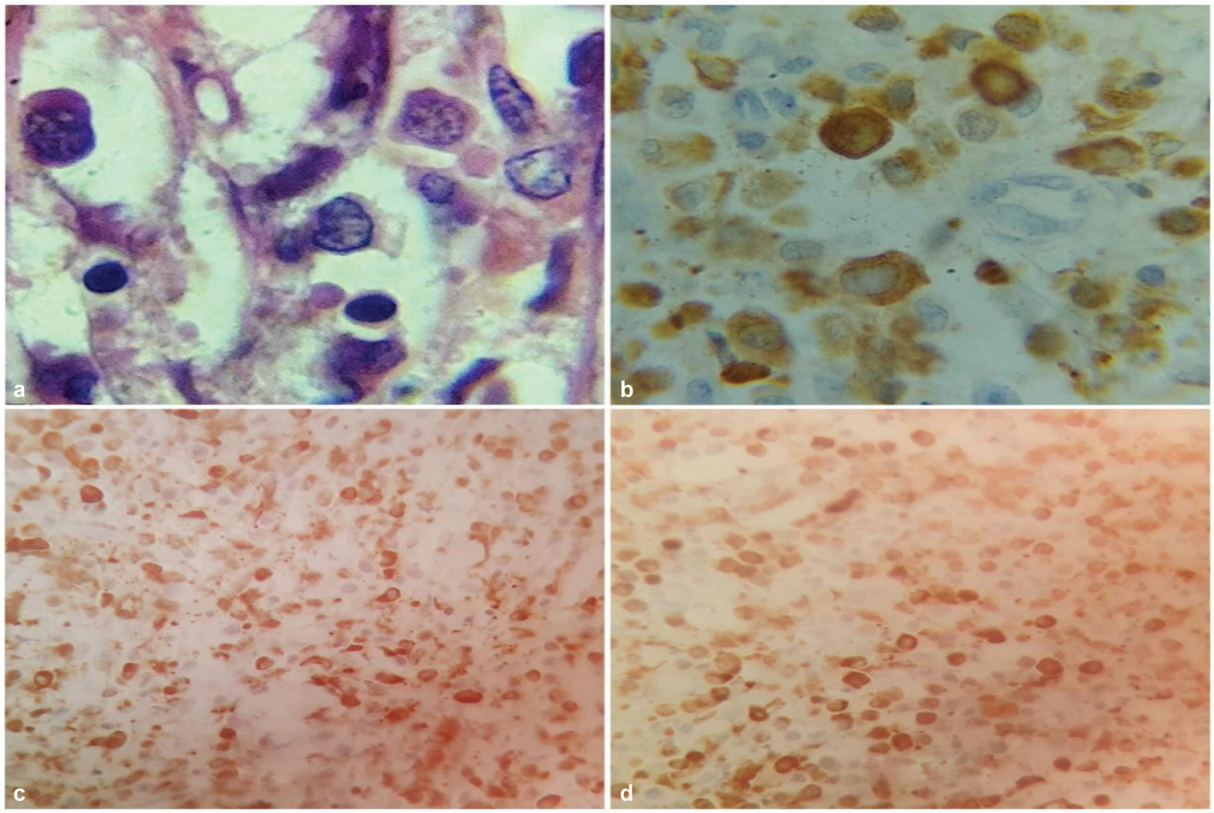

Fig. 3 (**a**) Presence of myeloblast cells having multilobated, vesicular nucleus, with prominent nucleolus with finely dispersed nuclear chromatin and scattered mitotic figures. (**b–d**) Immunohistochemical staining shows positive for Cluster of Differentiation 68, lysozyme, and myeloperoxidase, respectively.

succumbed after receiving seven courses of chemotherapy while admitted to the indoor patient department.

Discussion

GS is a malignant neoplasm formed by progenitor cells of granulocytic lineage. It is believed to originate from the bone marrow, reaches the subperiosteum through Haversian channels, and spreads elsewhere. The head and neck region is involved in 12 to 43% of the cases.[9] Oral GS affects a wider age group comprising both males and females. Only 89 cases have been reported in the English literature to date.[10] Commonly involved sites were the gingiva (40.6%), mandible (21.9%), and hard palate (15.6%). Only a few involved the lip, buccal mucosa, and other sites.[7] This case involved the mandible, which is consistent with what was reported by the previous authors.

Diagnosis of oral GS is difficult, especially when it presents as an isolated finding with no history of hematological disorders or bone marrow involvement.[9] This type is called isolated, primary, or nonleukemic GS.[3] The case initially showed no abnormality in bone marrow and peripheral blood count.[9] Authors have stated that histologically, GS presents as round to ovoid pleomorphic hyperchromatic cells arranged in sheets. They have round to oval nucleus with dispersed chromatin and prominent nucleolus.[6,9] Similar features were also noted in our case. Due to poor myeloblastic differentiation, the histopathological evaluation by H & E alone can be difficult resulting in erroneous diagnosis. In such cases, IHC staining, immune phenotyping along with flow cytometry may help in a definitive diagnosis.[9]

Alexiev et al have reported that the neoplastic cells of GS show reactivity with CD68, lysozyme, and MPO.[11] In our case, the neoplastic cells were CD68, lysozyme, and MPO positive confirming granulocytic lineage rather than lymphoid one, and thus, the overall IHC study was confirmative of GS. LCA is usually positive in GS; however, the authors have reported negative LCA in a few cases too,[12] which was corroborative to our finding. Flow cytometric immunophenotyping is useful to identify additional myeloid antigens, such as CD11, CD4, human leukocyte antigen—DR, CD13, CD33, CD45, CD56, and CD117, as well as antigens associated with immaturity, such as CD34.[13] The most frequent genetic mutations noted in GS are KIT (16.6%), followed by TET2 (14.6%), NRAS (14.6%), FLT3-ITD (12.5%), NPM1 (8.3%), and DNMT3A (6.2%).[14]

According to the literature, PET/CT has better accuracy than CT alone in diagnosis. GS lesions show elevated fluorodeoxyglucose uptake which changes with progression of treatment, thus affecting treatment outcome.[9] But in this case, no evidence of metabolically active disease or distance metastasis was noted when the PET/CT was done.

The treatment of GS depends on the site of the disease, initial diagnosis or relapse, the performance status, and the

age of the patient. Radiotherapy with chemotherapy is preferred for symptom relief and consolidation therapy.[7] According to the literature, most patients undergoing surgery alone generally relapse or progress to acute myeloid leukemia (AML). Thus, surgery should only be considered before systemic treatment in acute cases helping in rapid debulking and symptomatic relief.[3] However, there is an absence of a treatment guideline for primary GS with the recommended treatment method being a conventional AML-type chemotherapeutic regimen. In recent years, bone marrow transplantation and hematopoietic stem cell transplantation have been introduced in the treatment protocols which are being used in combination with radiotherapy and chemotherapy. Targeted therapy is a new aspect of primary GS treatment. The agents used are histone deacetylase inhibitors, DNA methyltransferase inhibitors, FLT3 inhibitors, and farnesyl transferase inhibitors.[1,7] In our case, the patient underwent hemimandibulectomy and proceeded with chemotherapy.

Misdiagnosis is common in patients with GS who have no symptoms of AML. These nonleukemic patients develop AML with 5 months to 1 year even after surgical resection or radiation therapy, thus making the prognosis worse. Average progression-free survival is around 12 months, the average survival rate being around 32 months, and 3-year survival rate is 41%.[15] The patient discussed here also died after 5 months while receiving chemotherapeutic regimen. With the development of cytogenetics and molecular biology, hypomethylating agents, targeted drugs, and immunotherapy have been shown to be effective.[14] The most common causes of death for MSs are infection, postoperative bleeding, and hernia of the brain due to the short-term enlargement of the tumor.[16] Our patient had clinical–radiological features similar to osteomyelitis, which led to the initial erroneous diagnosis and treatment. Therefore, early and accurate diagnosis can increase the life expectancy of these kind of patients.

Conclusion

GS is an uncommon neoplasm, the primary occurrence of which is quite unusual in the oral cavity. Diagnosis is challenging as it has to be differentiated from an array of other lesions such as lymphoma or other round cell tumors. Interpretation through all clinical, radiographical, histopathological, and IHC studies should be considered for early and accurate diagnosis of such cases where effective initiation of treatment can improve the patient's lifespan. Therefore, we should broaden our spectrum of differential diagnosis for the better life expectancy of the patients.

Authors' Contribution

L.P. and R.P.C. contributed to the conceptualization. L.P., S.B., R.P.C., and A.M. contributed to the design and definition of intellectual content. L.P., S.B., A.M., and S.S. contributed to the literature search. All authors contributed to the data acquisition and manuscript editing. L.P., S.B., and S.S. contributed to the manuscript preparation. L.P., S.B., and R.P.C. contributed to the manuscript review. L.P. is the guarantor.

If the Manuscript Was Presented as Part at a Conference/Convention/Meeting

Nil.

Declaration of the Patient Consent Form

Consent was taken and the document was attached separately.

Source(s) of Support in the Form of Grants, Equipment, Drugs

Nil.

Conflict of Interest

None declared.

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