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Submandibular Myeloid Sarcoma: An Ent Perspective

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Myeloid sarcoma (MS) is a rare form of extramedullary-site myeloid solid tumor composed of granulocytes and/or monocytes with variable degree of maturity and differentiation [1] [2]. It is also described by the terms granulocytic sarcoma, myeloblastoma and extramedullary myeloid cell tumor [3]. In literature, the diagnosis of myeloid sarcoma is closely associated with the one of acute myeloid leukemia (AML) with an estimated prevalence of 2 to 8% [4] and the one of myeloproliferative disorder with an even lower prevalence [1]. In both cases, myeloid sarcoma represents a blastic form transformation. There are very few cases of de novo diagnosis of myeloid sarcoma reported in literature.

At the Department of Otolaryngology of the San Camillo Forlanini Hospital in Rome, a 60-year-old Caucasian patient was seen on an outpatient basis for incidental finding of an asymptomatic left submandibular tumefaction, which had arisen about two months earlier. On remote pathological history she reported Hashimoto's thyroiditis, COPD, bronchiectasis and previous hepatitis B in remission. On family history, there were no neoplastic diseases. On objective examination, a neoformation of hard-elastic consistency, with sharp margins, fixed to deep planes, covered by eutrophic skin was appreciated. Ultrasonography showed a hypoechogenic solid formation measuring 17.1 x 16.1 mm adjacent to the left salivary gland in paramedian location with peripheral and intralesional vascularization on echocolordoppler and routine hematochemical examinations in the normal range. Head and neck (HN) CT examination with contrast medium identified the presence of solid oval-shaped neoformation of size 22 mm DAP x 17 mm DT x 22 mm (Figures 1) with clear margins compressing the outer contour of the left submandibular gland, from which it retains a cleavage plane, and presenting mild enhancement after administration of iodinated agent.

In addition there were some nonspecific reactive lymph nodes in laterocervical location bilaterally of paracentrimetric size. Indication was therefore made for FNA core biopsy, which showed morphophenotypic findings suggestive of lymphoproliferative pathology that, together with the paucity of material and heterogeneity of the lymphocyte population (diffuse infiltrate of medium-sized elements with irregular nucleus CD45+. Bcl2+, CD20+, focal nodular areas of small B lymphocytes, fractionated T lymphocytes, Bcl 6+ elements and fragments of dendritic meshwork from residual germinal center) posed an indication for excisional biopsy.

Once excised, the 2.5 x 2.1 x 1.6 sized nodule appeared macroscopically capsulated. Histopathologic examination described a lymph node with architecture subverted by a diffuse proliferation of cells with blastic habitus, having phenotype shown in Table 1 and small nodules containing cells with monocytoid habitus with phenotype in Table 1. The proliferation index was referable to 40 %. The morpho-phenotypic findings were consistent with the diagnosis of MS with partial monocytic differentiation.

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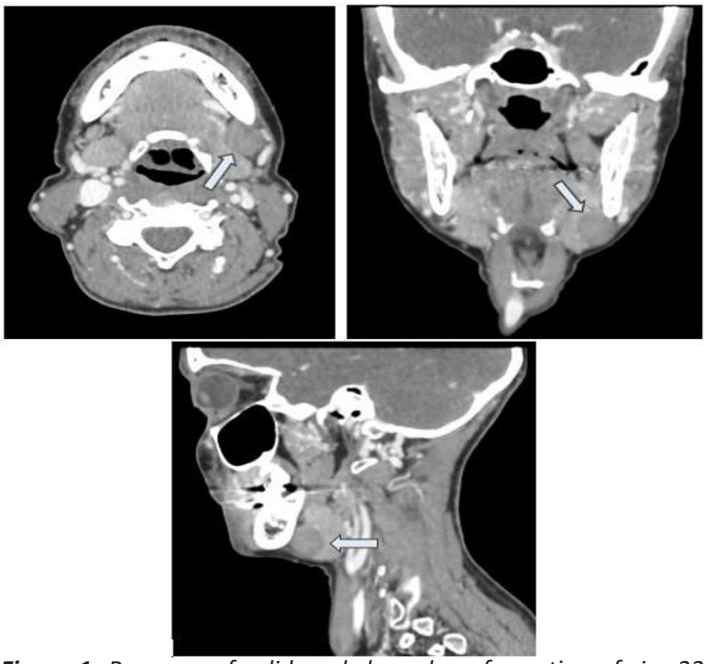

Figure 1: *Presence of solid oval-shaped neoformation of size 22 mm DAP x 17 mm DT x 22 mm with clear margins compressing the outer contour of the left submandibular gland, from which it retains a cleavage plane, and presenting mild enhancement after administration of iodinated agent.*

The patient was therefore referred for hematologic evaluation, where she performed diagnostic completion with bone marrow (BM) biopsy. Histologic examination showed normocellularity for age (BM cellularity at 40%) in the absence of AML, preserved myelo/erythroid ratio at normo-maturing lines, CD34+ blasts and small blasts less than 5% of BM cellularity. She also performed BM needle aspiration for:

Morphology: hypocellular marrow. Myeloid series present in all maturational stages and normomature to neutrophilic granulocyte. Erythroid series present in more mature forms. Megakaryocyte series normorappresent and in normal plateletopoietic activity. Undifferentiated elements (medium size, nucleated, basophilic cytoplasm, high nucleus/cytoplasmic ratio, lax chromatin) 2% within limits;

Immunology (negative), cytogenetics (46, XX negative), standard molecular biology and NGS (both negative).

Therefore, it was decided to nominate the patient for conventional induction chemotherapy according to 3+7 schedule (daunorubicin for 3 days, cytarabine for 7 days) and was addressed to BM transplantation, whose donor is her brother, afterwards

MS is classified in the WHO classification as one of the subgroups of myeloid neoplasms and acute leukemia [2]. It represents extramedullary proliferation of immature myeloid cells (blasts) with partial or complete subversion

Table 1: *Proliferating cells phenotype.*

Positive markers	Negative markers
CD 45+	CD34 -
MPO +	CD10 -
CD117 +	CD20 -
Bcl2 +	CD3 -
MUM1 -	Pax5 -
c-Myc +	CD79a -
	Bcl6 -
monocytoid habitus cells	CD123 -
MPO +	CD56 -
CD117 +	CKAE1/AE3 -
CD68PGM1 +	CK20 -
	MART1 –

of the developmental site architecture that typically form tumor masses [5]. It is globally considered an extremely rare disease [6-10] that can present as an isolated extramedullary leukemic tumor [2] with a higher incidence in children of 30%, compared with 2.5% in adults [11].

It can present as the clinical manifestation of AML or more rarely of a myeloproliferative syndrome [2]. It may follow (up to 50% of cases), present concomitantly (35% of cases) or anticipate (approximately a quarter or cases) the development of leukemia [12-13] and in this case involvement of an extramedullary site would go before the one of the BM [5]. In some situations it may manifest as relapse after therapy (13), after stem cell transplantation [11] (mostly isolated MS) as reduced graft versus leukemia effet at extramedullary sites [14] or develop in the absence of AML [5] like isolated leukemic tumor [12]. Its pathogenesis seems related an aberrant homing signal for the leukemic blasts [2] with ability to invade the surrounding tissues and specific interaction between the matrix metallo-proteinase (MMP-9) and the leukocyte surface beta [15].

Higher expression of MMP-2 and membrane type 1 metalloproteinase in vitro study confirm the role of MMPs in extramedullary blast invasion [16]. Clinic is closely associated with the organ involved. It mostly develops within skin (the most common site in children [17], soft tissues, lymph nodes, and gastrointestinal tract [5], and the HN district is the second region of the body to be affected, after the torso and before the extremities [3]. For the HN district, the oral cavity is the most affected region [18]. MS involving the HN region can pose an insidious diagnostic challenge because of its low incidence, its nonspecific presentation [18], and the possibility that tumors of almost any type may occur in this district thus leading to a wide differential diagnosis [4, 11, 19 - 24]. At the time of diagnosis the size is highly variable ranging from 2 to 20 cm and the common presentation are compression signs accompanied

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by severe pain and abnormal bleeding [2]. Isolated forms with a wide heterogeneity of presentation are described in the literature: salivary gland, neck lymph nodes [8] and cervico-mediastinal masses [25].

Any neck mass in adult is often misdiagnosed and require immediate attention because differential diagnosis of lateral neck masses is vast (congenital, inflamed, reactive structure, salivary gland pathology, traumatic) and includes metastatic dissemination or primary malignancy [26], like lymphoma, undifferentiated cancer, malignant melanoma, extramedullary hematopoiesis [10]. Differential diagnosis should include non-Hodgkin lymphoma, blastic plasmacytoid dendritic cell neoplasm, histiocytic sarcoma, melanoma, carcinoma, and (in children) small round blue cell tumors [5]. Cases of initially misdiagnosed as T-cell lymphoma are also described [27]. Due to the In case the diagnosis of MS is de novo, we face a serious difficulty in terms of differential diagnosis. In fact, morphologically there are many similarities with other hematologic malignancies including B-cell lymphoma. This is particularly evident in cases of immature MS, in which no evidence of differentiation is observed. Therefore, it is always recommended to perform a minimum antibody panel including anti-CD43, anti-lysozyme, CD33, myeloperoxidase, CD34, CD117 [5], CD3, CD20 [27] and CD68/KP1, the most commonly expressed marker (100%) [10].

The report cases of MS involving salivary gland are few [6] with only 17 cases (10 parotid gland, 6 sudmandibular gland, 1 both) of which just 4 are isolated (1 parotid gland 3 submandibular gland) and the remaining 13 affected by various other lesions [8] like preexisting sebaceous lymphadenoma in the parotid gland. Diagnosis is often subsequent to a simple FNA biopsy in cases of previous diagnoses of myeloid neoplasms [9]. It has an extremely rare presentation without any prior history of myeloid neoplasm [2] [9] [10]. BM involvement is a common prerogative of all patients with isolated MS with a mean interval of 10 months [28]. In our case this was negative after BM biopsy. Histologically, 50% of the tumors were of the blastic type, 43.5% either monoblastic or myelomonocytic and 6.5% corresponded to different histotypes [10]. Isolated MS is most commonly a recurrence of patients undergoing allogeneic stem cell transplantation (8-20%) [29]. The reasons for this event are currently unclear [28]. Only one case of de novo MS developed just at the level of the left submandibular region is reported in the literature, extremely large with facial disfigurement (left side submandibular, sublingual salivary gland left parotid, left side masseter muscle, myeloid muscle, and left side medial pterygoid muscle). Asymptomatic female in her late 30s from North Africa with no past medical history with expanding left face and neck mass is initially identified as highgrade T-cell lymphoma and later, upon review of immunohistochemical study, updated with the diagnosis of MS. BM biopsy is negative [27].

A retrospective reading shows the multiple peculiarities of this case: the diagnosis on infiltrating soft tissue enhancing mass surrounding left submandibulary gland, the silent symptomatology, and the absence, both at discharge and at diagnostic completion with BM biopsy, of AML. The behavior of MS was dramatic irrespective of presentation, age, sex, phenotype and cytogenetics [10]. Hovewer literature suggests that patients with isolated MS may have a better prognosis compared with AML patients without it [2]. This case shows the need for multidisciplinary collaboration among specialists (sonographers, neuroradiologists, anatomo-pathologists, otolaryngologists, oncohematologists) to correctly define the diagnostic and therapeutic pathway of "difficult" diseases of the HN district.

Conclusions

MS is a pathology that has been described for more than two centuries, but its rarity and correlations with acute myelodie leukemia remain undefined. Isolated MS is most commonly a recurrence of patients undergoing allogeneic stem cell transplantation with a wide heterogeneity clinical presentation. This case present multiple litterature peculiarities: the infiltrating soft tissue enhancing mass without involvment of submandibulary gland, the silent symptomatology and the absence of active myeloid leukemia.

Multidisciplinary collaboration is always recommended for the diagnosis of neck mass, especially in difficult case.

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