Head and Neck Extranodal Interdigitating Dendritic Cell Sarcoma: Case Report and Review of the Literature

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Abstract Interdigitating dendritic cell sarcoma (IDCS) is an exceedingly rare neoplasm originating from professional antigen presenting cells normally located in the T zone of the lymph node. The purpose of this report was to describe the first case of the IDCS of the submandibular gland and perform a review of the literature of head and neck IDCS. We present a case of an 81-year-old man with a 5 months history of slowly enlarging painless mass in right submandibular region. Fine needle aspiration cytology was suggestive of squamous cell carcinoma. The patient underwent surgical resection of the right submandibular gland and neck dissection. A malignant spindle cell proliferation involving the submandibular gland and colonizing one laterocervical lymph node was found. Morphology and immunophenotype prompted a differential diagnosis of a metastatic spindle cell melanoma versus an IDCS. Transmission electron microscopy was performed and supported a diagnosis of IDCS. The diagnosis of IDCS is a challenging task and may require a large array of techniques.

Keywords Interdigitating dendritic cell sarcoma · Submandibular gland · Transmission electron microscopy · Head and neck cancer · Diagnosis · Therapy

Introduction

Interdigitating dendritic cell sarcoma (IDCS) is an exceedingly rare neoplasm originating from professional antigen presenting cells normally located in the T zone of the lymph node [1, 2]. Only about one hundred cases of IDCS are reported in the English literature. The most frequently involved primary sites are lymph nodes, mainly in cervical and axillary regions. Extranodal localizations have been described in liver, lung, spleen, digestive system, bone marrow, and head and neck sites [3].

Up to to date, 12 cases of extranodal head and neck IDCS have been described: three in the parotid gland [4–6], three in the tonsil [7–9], three in the nasopharynx [10–12], one in the nasal cavity [13], one in the alar cartilage [14], and one in the oral cavity [15]. The low incidence rate and the particular features of this neoplasm make the diagnostic and therapeutic process a real challenge for the clinicians.

We present a case of IDCS localized in right submandibular gland.

Clinical History

An 81-years-old man presented to our institution with a 5 months history of slowly enlarging painless mass in right submandibular region without other symptoms. Ear, nose, and throat examination was negative. Computed tomography (CT) scan revealed an enlarged right submandibular gland as compared with the contralateral one (maximum

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diameter of 45 vs 40 mm) with a swelling of the lower pole (about 20 mm) and irregular and necrotic lymph nodes, with maximum size 2.5 cm, within the levels Ib, IIa and IIb; moreover a lymph node of IIb level had a compressive effect on the internal jugular vein (IJV). F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) showed abnormal uptake in the right submandibular gland (Standardized Uptake Value-SUV 8.6) and in the ipsilateral cervical nodes (SUV 8.5). Fine needle aspiration cytology of the submandibular mass was performed that was initially resulting suggestive of squamous cell carcinoma.

Since either metastases from unknown primary tumor or alternatively a carcinoma of the submandibular gland metastasizing in the neck nodes were suspected, resection of the right submandibular gland and ipsilateral neck dissection (level I–V with sacrifice of IJV) were performed. During surgery it was necessary to sacrifice the marginalis mandibulae nerve and the hypoglossal nerve because they were respectively encased in the submandibular mass and in the II level lymphadenopathy.

After definitive histopathological diagnosis of IDCS, the patient underwent conventional fractionated radiotherapy up to a dose of 60 Gray. A neck and chest CT scan performed 2 month after the end of the radiotherapy showed no recurrence of disease, the subsequent follow-up period of 8 months was clinically uneventful.

Nine months after the end of radiotherapy, the patient was hospitalized for constipation and icterus. A CT scan diagnosed an advanced pancreatic neoplasm with liver metastasis. A biopsy of the neoplasm was not carried out because there were no therapeutic chances, due to the advanced stage of disease and to the general conditions of the patient. The patient died 2 months later.

Materials and Methods

The surgical specimen was fixed in 10 % buffered neutral formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin. Immunohistochemical stainings were performed on paraffin sections of formalin-fixed tumor tissue and according to standard laboratory procedures [16].

Molecular analysis of BRAF gene was performed using polymerase chain reaction to detect mutation of exon 15 and fluorescence in situ hybridization (FISH) analysis was performed using LSI EWSR1 Dual Color Break Apart Rearrangement Probe (Vysis) to assess the EWS gene rearrangements.

Tumor tissue fragments for transmission electron microscopy (TEM) were obtained from the formalin fixed surgical specimen. Post fixation was performed in 1 % OsO₄ in 0.1-mol/L veronal acetate buffer (pH 7.4) for 1 h.

The tissue samples were stained en bloc in 2 % uranyl acetate in 50 % ethanol, dehydrated in increasing concentrations of ethanol, cleared in propylene oxide, embedded in epoxy resin and cut, using a diamond knife, with a Leica Ultracut R microtome. Ultrathin serial sections were mounted on formvar-coated Cu/Rh grids, stained with uranyl acetate and lead citrate, and observed with a Philips 410 LS TEM instrument.

A review of the literature looking for reported cases of extranodal IDCS of head and neck region was conducted using PubMed, including Mesh terms and manual searches.

Results

Gross and Microscopic Findings

The specimen consisted of a right submandibular gland (dimension 5 × 4 × 3 cm) containing a single firm nodule 4.5 cm in diameter in the salivary parenchyma.

The histological examination revealed an intra-parenchymal neoplasm with peritumoral lymphocytes (Fig. 1a). Within the neoplasm, no preexisting lymph node was found. The neoplasm consisted of a proliferation of atypical spindle cells with abundant slightly eosinophilic cytoplasm with indistinct border with clear nucleus and evident nucleolus (Fig. 1b). Foci of necrosis were present, too (Fig. 1b–d). The resection margins were not involved by the neoplastic proliferation. One of the II level lymph nodes (maximum diameter 2.2 cm) was involved by IDCS. The lymph node was not adjacent to the gland.

Immunohistochemical Findings and Cytogenetic Findings

Immunohistochemical studies showed diffuse positivity for S-100 (Fig. 1c, d) and vimentin, whereas immunoreaction for CK-AE1/3 and calponin were limited to rare cells. All other tested markers (p63, CD21, CD35, CD4, GFAP, MELAN-A, MITF1, HMB-45, CK5, CK-MNF116, CK-CAM 5.2, EMA, clusterin, CD1a, CD68, langerin) were negative (Table 1). Both the research of BRAF gene mutations and the cytogenetic molecular FISH analysis for EWS gene mutation were negative. Considering the histological and immunophenotypic characteristics, a localization of malignant spindle cell melanoma was the first diagnostic hypothesis, alternatively an IDCS was suspected.

Electron Microscopic Findings

A diagnosis of IDCS was formulated based also on the features of TEM study which displayed: large spindle cells, with irregular nuclear edges and prominent nucleoli, thin

Fig. 1 **a** The tumor is intraparenchymal, peritumoral lymphocytes are present. No pre-existing intraparenchymal lymph node is evident (original magnification: $\times 40$). **b** The tumor is composed of spindle shaped cells of medium and large size, with abundant eosinophilic cytoplasm. The nucleus is clear with evident nucleolus (original magnification: $\times 400$). **c** Neoplastic cells are positive for immunohistochemical staining for S100 protein. A nerve is present (original magnification: $\times 200$). **d** Neoplastic cells are positive for immunohistochemical staining for S100 (original magnification: $\times 400$).

e Large spindle cells, with irregular nuclear edges and prominent nucleoli, thin extensions of the membrane, immature junctions between adjacent cells, cytoplasm with abundant rough endoplasmic reticulum and Golgi vesicles. The neoplastic cells showed complex interdigitating cell processes without well-formed desmosomes (original magnification: $\times 4400$). **f** Interdigitated extensions containing mitochondria, lysosomes and abundant intermediate filaments. Neither granules Birbeck, nor joints, nor melanosomes are observed (original magnification: $\times 14,000$)

extensions of the membrane, immature junctions between adjacent cells, cytoplasm with abundant rough endoplasmic reticulum and Golgi vesicles. The neoplastic cells showed

complex interdigitating cell processes without well-formed desmosomes (Fig. 1e). Neither melanosomes nor Birbeck's granules were found (Fig. 1f).

Table 1 Immunohistochemical panel

Antigen	Result
S100	+
Vimentin	+
CK-AE1/3	–/+
Calponin	–/+
p63	–
CD21	–
CD35	–
CD4	–
GFAP	–
MELAN-A	–
MITF1	–
HMB-45	–
CK5	–
CK-MNF116	–
CK-CAM 5.2	–
EMA	–
Clasterin	–
CD1a	–
CD68	–
Langerin	–

+, positive; –/+, limited to rare cells; –, negative

Review of the Literature

A review of the literature through searches of PubMed and Medline databases, including Mesh terms and manual searches, was performed to identify all reported cases of extranodal IDCS of the head and neck region with no limitations on year of publication. The results are summarized in Table 2.

Discussion

Dendritic cells are structural and immune accessory cells contained in peripheral lymphoid organs. A subtype of dendritic cells are represented by interdigitating dendritic cells (IDCs), which are highly specialized immune accessory cells that present antigens to T cells and regulate cellular immune response. IDCs are derived from the hematopoietic stem cells from bone marrow [17] and are localized in T-zones of lymphoid organs such as paracortex and deep cortex of lymph nodes, Waldeyer's ring, interfollicular areas of mucosa associated lymphoid tissue and periarteriolar lymphoid sheaths in spleen [2, 12]. Other dendritic cells subtypes are follicular, Langerhans and histiocytic/fibroblastic cells [18]. Tumors arising from dendritic cells are very uncommon, accounting only 1 % of

hematolymphoid malignancies [2, 19]. Follicular dendritic cell sarcoma is the most frequent dendritic cell malignancy with 343 cases described in the literature. On the other hand, only 100 cases of IDCS have been reported [3].

In the head and neck region IDCSs have frequently a lymph node localization (41 cases described) [3]. Conversely, the extranodal involvement is quite rare (13 cases, including the one hereby described). In six cases the primary site was found in the Waldeyer's ring, which is consistent with the high presence of lymphatic tissue and IDCs in this area.

Extranodal IDCS cases of the head and neck region affect adult patients (median age 54.5 years, range 23–87) with a female predilection (F:M = 7:5). The review of the literature reveals that a painless swelling without other related symptoms is the most common symptom of presentation. Two cases [10, 12] with nasopharyngeal localization revealed multiple neurological involvements, such as a complete ophthalmoplegia with ptosis in one patient [10] and diplopia, ataxia, right-sided facial nerve paresis and hypoguesia in the other one [12]. These neurological symptoms are probably due to compressive effect of the mass on cranial nerves and to the skull base involvement. In a case of IDCS localized in nasal cavity described by Lee et al. [13], the patient presented nasal obstruction and frequent blood-tinged crust. Systemic symptoms as fever, weight loss, night sweats and chills are sometimes related to nodal IDCS, but they have not been described in extranodal IDCS of head and neck.

In the present case, the patient also had a lymph node localization of disease. In the series of extranodal head and neck IDCSs, a lymph node involvement beyond the primary site was described in four other cases [5, 9, 10, 12]. This clinical pattern is currently interpreted as due to metastasis [3]. The diagnosis of IDCS requires a high index of suspicion, use of suitable markers, and multiple diagnostic tools. In 11 % of all previously described cases, the initial pathological diagnosis was incorrect [3]. Concerning head and neck extranodal IDCS, the tumor was initially confused with malignant melanoma, undifferentiated carcinoma, and atypical lymphoproliferative lesion [6, 9]. Histologically, IDCSs consist of a proliferation of spindled to ovoid cells, usually arranged in a storiform or a whorled pattern. The cytoplasm is abundant, slightly eosinophilic, and often with an indistinct border. Nuclei are clear with small to large nucleoli. Immunohistochemically, neoplastic cells are constantly positive for S100 protein and vimentin and consistently negative for CD1a, langerin, CD21, CD23, and CD35. The absent expression of both specific Langerhans cells' histiocytic markers and follicular dendritic cells' markers is relevant for the differential diagnosis. Unlike the other subtypes of dendritic cells tumor, IDCS presents positivity with CD68 and S100 and absence

Table 2 Reported cases of extranodal IDCS of head and neck region

References	Gender	Age	Site	Treatment	Follow-up
Barwell et al. [4]	F	51	Parotid	Surgery	24 months. NED
Sharma et al. [5]	M	73	Parotid, cervical lymph nodes	Surgery + PORT	15 months. NED
Efune et al. [6]	M	69	Parotid	Surgery + PORT	12 months. NED
Jayram et al. [10]	F	33	Nasopharynx, cervical lymph nodes, distant metastases (pleura and liver)	CT	Rapid progression of disease. Death 3 months after diagnosis
Turner et al. [11]	M	30	Nasopharynx	RT	Alive after 13 months with disease
Dunlap et al. [12]	M	35	Nasopharynx, bilateral cervical lymph nodes	RT and CT	After 20 months duodenal recurrence treated with RT
Parada et al. [14]	F	87	Alar sidewall nasal area	Surgery	No data
Lee et al. [13]	F	73	Nasal cavity	Surgery + PORT	18 months. NED
Androulaki et al. [7]	M	55	Tonsil	Surgery	6 months. NED
Gaertner et al. [8]	F	77	Tonsil	Surgery + PORT	5 months. NED
Kim et al. [9]	F	56	Tonsil, cervical lymph nodes	Surgery + POCRT	No data
Martins et al. [15]	F	50	Oral cavity	Surgery	No data

IDCS interdigitating dendritic cell sarcoma, RT radiotherapy, CT chemotherapy, POCRT post-operative concurrent chemoradiotherapy, PORT post-operative radiotherapy, NED no evidence of disease

of Birbeck granules [3]. In the case presented by Martins et al. [15], the immunophenotype of the oral cavity tumor was compatible both with IDCs and with intermediate dendritic cells sarcoma, demonstrating possible overlapping features of these two entities. TEM was used in four cases [5, 8, 11], included the present case, and it was relevant to render the definitive diagnosis of IDCS. The key diagnostic ultrastructural feature is the presence of elongated cytoplasmic processes devoid of an external basal lamina, in absence of desmosomal junctions, melanosomes, and Birbeck granules. TEM is an extremely important technique for soft tissue tumors diagnosis; unfortunately, its availability and employment has decreased in recent decades and most of pathology departments use immunohistochemical markers for the diagnosis. However, a large panel of immunohistochemical marker usually permits to exclude all the other differential diagnoses, allowing to formulate a diagnosis of IDCS [4, 6, 7, 9, 10, 12–14].

In the present case, both the research of BRAF gene mutations, whose mutations are found in about 60 % of melanoma [20], and the cytogenetic molecular FISH analysis for EWS gene rearrangement, involved in many types of sarcoma, were negative. Remarkably, and unlike other histiocytic and dendritic cell neoplasms, IDCSs are not reported to harbor BRAF mutations [21, 22].

CT scan with contrast medium is the most frequently used imaging tool to define the size and the location of disease though this neoplasm does not have specific radiological features. 18-FDG PET was used only in three cases of head and neck extranodal IDCS [9, 12], included the one presented here. IDCS presented in all cases a significantly high SUV.

Since IDCS is a rare neoplasm, there are no guidelines regarding the treatment. Four cases of extranodal head and neck IDCS with resectable disease were treated with surgery and six cases with surgery followed by radiotherapy. Exclusive radiotherapy, intensity modulated radiation therapy followed by systemic chemotherapy and systemic chemotherapy alone were used in the cases of nasopharyngeal IDCS described respectively by Turner et al. [11], Dunlap et al. [12] and Jayram et al. [10]. In 10 cases of extranodal IDCS of head and neck data about follow up are available, with a mean time of 12.5 months (range 3–24 months). In 7 cases, all treated with surgery ± radiotherapy, a complete response with negative follow-up was observed (mean 12.4 months, range 3–24 months). In the case described by Turner et al. [11], the patient was still alive with disease 13 months after the end of radiotherapy; in the one described by Dunlap et al. [12] the patient developed a duodenal recurrence 20 months after the end of chemoradiotherapy,

successfully treated with radiotherapy. In another case [10] the patient presented pleural and hepatic localization at the moment of the diagnosis and had a rapid progression of disease that caused the death in 3 months. Surgery seems to be the better treatment in case of localized and resectable disease, and, as highlighted in a recent review [3], adjuvant radiotherapy does not seem to significantly improve overall survival. Systemic chemotherapy is the mainstay of treatment in IDCS patients with distant metastases. Exclusive radiotherapy may be used in case of localized unresectable disease [3].

The clinical course of IDCS is unpredictable and ranges from indolent to aggressive with a high propensity for distant metastases being found in about one-third of patients [23]. Stage at the presentation is the most important prognostic factor but also young age seems to have a negative impact [3]. It is hypothesized that this may be attributed to the high activity of antigen presenting system in young individuals which decreases in elderly [24]. In the series of extranodal IDCS of head and neck, the three younger patients presented a nasopharyngeal localization of IDCS and had the worst prognosis; two of them [10, 12] developed distant metastases and one [11] did not achieve complete response after radiotherapy.

Conclusion

IDCS of head and neck do not differ from IDCS of other sites in terms of clinical behavior and morphological features. The pathologist and the clinician have to be aware of its possible occurrence in head and neck region due to the high presence of nodal and extranodal lymphatic tissue in this area. This rare and intriguing entity requires a high index of suspicion and the use of a large panel of diagnostic tools, possibly including also TEM. Achieving a correct diagnosis of IDCS is clinically relevant considering that this malignancy may be successfully approached with surgery with or without adjuvant radiotherapy.

Conflict of interest None declared.

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