Case Report

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Castleman's disease of a submandibular mass diagnosed on Fine Needle Cytology: Report of a case with histopathological, immunocytochemical and imaging correlations

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Summary **Castleman's disease (CD) is an unusual inflammatory lymphoproliferative disorder of uncertain aetiology, mainly involving lymphatic tissue in the mediastinum, but also occurring in the neck, lung, abdomen, pelvis, skeletal muscle and retroperitoneum. Fine Needle Cytology (FNC) is a quick, cost-effective and safe diagnostic modality to investigate on organs involved by CD, also providing a guide to treatment and management of patients with lymphoadenopathy. We report a case of a 44-year-old man who underwent FNC of a submandibular mass with subsequent surgical excision. Cytology revealed an atypical lymphoproliferative process, which arose the suspicion of CD. Histopathological study of the excised masses combined with immunhistochemistry and imaging of the submandibular and neck areas, confirmed the suspicion. A final diagnosis of Unicentric Castleman's disease, hyaline-vascular type, was made.**

Keywords: Lymphoproliferative disorder, aspiration cytology, hyaline vascular type

1. Introduction

Castleman's disease (CD) was firstly described in 1956 by Castleman and his collaborators in a group of patients with benign localised hyperplastic lymph nodes in the mediastinal area (*1*).

It is a rare lymphoproliferative condition of unknown cause, with the two main hypotheses being abnormal immune response and viral infection (*2,3*). The age of affected patients ranges from 8 to 69 (*4,5*), with no sex predilection (*5,6*). Although the disease is mostly located in the mediastinum, CD can occur wherever lymphoid tissue is found (*7,8*).

CD is divided into localized/unicentric (UCD) and generalized/multicentric (MCD) due to the profound clinical differences between the two variants. Patients with UCD are generally asymptomatic, with a painless solitary mass usually localized to the mediastinum or pulmonary hilum, although other locations like the pelvis, neck, abdomen, axilla and retroperitoneum have also been described (*9*). A minority of patients may present few symptoms, such as cough, dyspnea, fever, night sweats, peripheral lymphadenopathy, splenomegaly and hepatomegaly, depending on the histopathological subtype (*5,10*). UCD has a benign prognosis.

In contrast, MDC involves multiple lymph nodes separately or in a confluent pattern and patients present systemic symptoms including autoimmune phenomena and an aggressive course (*11*). MCD is frequently associated to HHV8 infection, Kaposi sarcoma and HIV infection (*12,13*).

Microscopically, two distinct histological patterns have been described: the hyaline-vascular type (HV) and the plasma cell type (PC). A third "mixed" type

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presenting histopathological features of both HV and PC types has also been reported (*3,14*).

Fine Needle cytology (FNC) is a useful, minimally invasive technique to obtain a preoperative diagnosis in many organ sites (*15*) and to rule out reactive lymphadenopathies and malignant lymphoma or other neoplastic conditions (*16-18*). Although the cytologic diagnosis of conditions that affect lymph nodes can be very challenging, the overall diagnostic FNC accuracy has been reported to be 90% approximately, with a sensitivity of 85-95% and specificity of 98-100% (*19,20*).

False-negative cytological diagnoses on lymph nodes are more common than false-positive, due to inadequate sampling, inexperience with their cytology and overlapping of morphological features (*20,21*). Therefore, ancillary techniques and/or excisional biopsy may be very helpful for a definitive diagnosis.

We report herein the cytomorphological features, based on FNC, of a case of UCD hyaline-vascular type correlated to imaging, immunocytochemistry and histological findings.

2. Case Report

In 2009 a 44-year-old male was admitted to a local hospital for the excision of a left submandibular lymph node. The diagnosis of reactive hyperplasia was made and confirmed by a later counselling at a hospital in Bologna. The patient was suffering from microcytic anemia with thrombocytopenia since childhood and had been splenectomised without success. In 2014 a painless and moderately hard lump appeared under the submandibular scar, measuring 5 cm in diameter, and he was then referred to our Institute.

FNC samples were obtained under palpation or ultrasound guidance by using 23-25G needles, without suction. The smears were air-dried and stained with Diff Quik™ or wet-fixed in 95% ethanol and stained with Papanicolaou (Pap). Immunocytochemistry was also carried out: the smears were stained for CD3, CD20, CD21, CD30 and Ki67.

A few days later the patient returned to our Institute for an ultrasound examination followed by surgical removal of the submandibular lymph node and a salivary gland. Immunohistochemistry was performed, using CD10, CD20, B-cell lymphoma 6 (Bcl6), B-cell lymphoma 2 (Bcl2), Ki67 protein on the lymph node sample and CD20, CD1, CD34, CD3, CD30, CD138, B-cell lymphoma 6 (Bcl6), B-cell lymphoma 2 (Bcl2), Ki67 protein on the salivary gland sample.

Since the operation, the patient showed no progression or recurrence of the disease during the follow-up.

2.1. *Cytological findings*

The submandibular lymph node smears showed a polymorphic cytological picture represented by lymphoid cells in different maturation stages, of both B- and T-cell type. The general impression was, nevertheless, that of a relative depletion of follicular centre cells, with numerous atypical lymphoid cells of medium to large-size, later found to be atypical follicular dendritic cells. These cells were characterised by a transparent cytoplasm, with indistinct dendritic processes on both Pap and DQ stained slides; they showed a single large, sometimes nucleolated, vesicular nucleus with homogeneously scattered heterochromatin (Figure 1A and 1B). Occasionally, bi- and plurinucleated atypical cells with similar nucleo-cytoplasmic features were also found (Figure 1C). Sporadic histiocytes were also observed; their cytoplasm engulfed with intact mature lymphocytes (Figure 1D). Thin capillary fragments were scattered among the cells (Figure 1E). Immunocytochemical staining showed a diffuse membrane positivity for CD20 in the lymphoid B-cells and for CD3 in the lymphoid T-cells. The atypical cells did not show any expression of CD30 but diffusely expressed CD21, which also enhanced their cytoplasmic

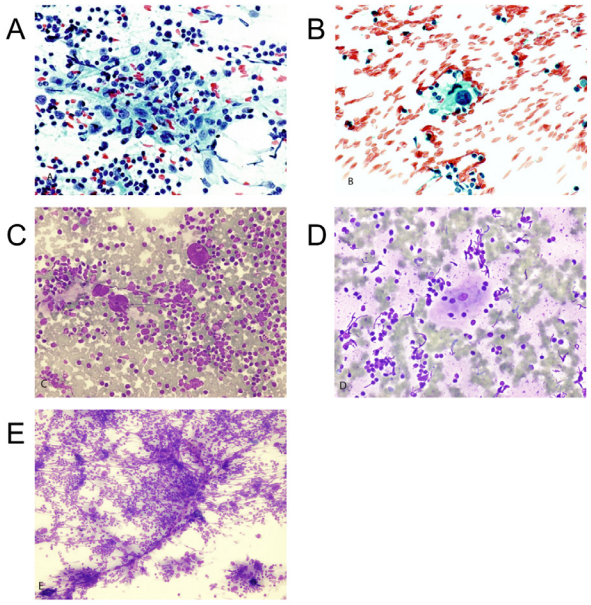

Figure 1. Cytological findings: FNC samples. (A) A sheet of large atypical lymphoid cells can be seen admixed with lymphocytes in various stages of maturation. The cells show oval nuclei with vesicular chromatin appearance. Scattered chromocenters and occasional nucleoli may be seen. (Pap, ×400, original magnification). **(B)** A single atypical lymphoid cell shows a large vesicular nucleus with rough chromatin pattern and a prominent nucleolus of irregular shape. Also notice the delicate, slightly cianophylic dendritic cytoplasmic extensions surrounding its nucleus (Pap, x630, original magnification). **(C)** Atypical follicular dendritic cells showing both a single large, nucleolated, vesicular nucleus with homogeneously scattered heterochromatin and bi/ plurinucleation (DQ, ×400, original magnification). **(D)** Histiocytes with cytoplasm engulfed with intact mature lymphocytes (DQ, ×400, original magnification). **(E)** Capillary fragments scattered among the cells (DQ, ×200, original magnification).

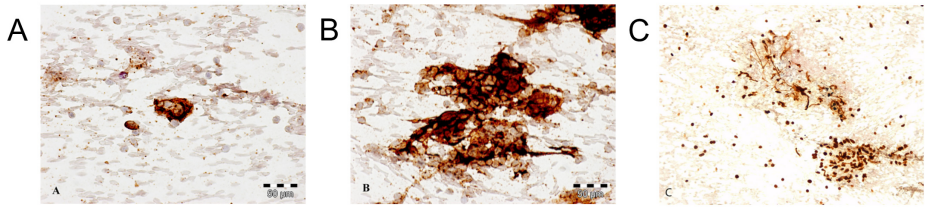

Figure 2. Immunocytological findings. (A) An atypical cell diffusely expressing CD21, which also enhanced its cytoplasmic dendritic processes (Immunoperoxidase, ×600, original magnification). **(B)** CD21 showed a diffuse positivity in the atypical cells as well as among the mature lymphoid cells (Immunoperoxidase, ×600, original magnification). **(C)** Ki67 staining ratio (Immunoperoxidase, ×200, original magnification).

dendritic processes (Figure 2A). CD21 also showed a diffuse interstitial positivity among the mature lymphoid cells (Figure 2B). Ki67 staining ratio was extremely high (almost 100%) (Figure 2C).

A cytological diagnosis of atypical lymphoproliferative disease was made. The possibility of Castleman's disease was also hypothesized and therefore surgical resection of the mass and its histopathologic examination were suggested.

2.2. *Imaging features*

Ultrasound examination of the left submandibular area showed a major hypoechogenic mass of 5 × 2.5 cm of diameter approximately, with regular margins and light internal lobulations (Figure S1A), and a few other adjacent masses less than 1cm of diameter. Color-Doppler examination showed both intralesional and peripheral vascularisation. Three other normal appearing lymph nodes between Level III (10 mm) (Figure S1B) and IV (10 and 12 mm) (Figure S1C) of the neck were also detected.

No signs of further submandibular, laterocervical or supraclavear lymphadenomegaly were found. Computed tomography of the thorax and abdomen revealed no suspicious masses.

2.3. *Histological findings*

Lymph node of the II left submandibular Level. Histopathology revealed a well-preserved lymph nodal structure formed by germinal centres surrounded by thick mantle zones (Figure S2). Germinal centres were immunochemically positive for CD10, CD20, Bcl6 (but no positivity was detected in the interfollicular areas) and negative for Bcl2. The Ki67 proliferative index was very high (90%). These findings were compatible with a reactive lymphadenopathy.

Left submandibular scialectomy. The scialectomy sample consisted of a mass of 7 × 4 × 3 cm with an annex fibro-fatty fragment containing the submandibular salivary gland of 5 × 3 × 2.5 cm. The mass was capsulated, with a gray-whitish cut surface and surrounded by an irregular paler area of 1 cm in diameter. A lymph node measuring of 2 × 1 cm was also present in the periphery of the

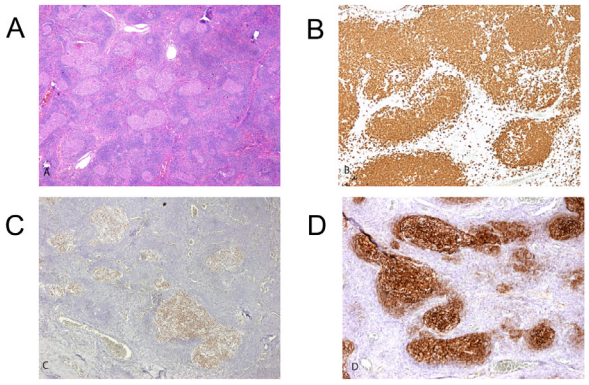

Figure 3. Microscopic and immunohistochemical examination of the left submandibular scialectomy. (A) Microscopic appearance of the lymph node (HE, x40, original magnification). **(B)** The lymph node was characterised by enlarged follicular structures immunochemically positive for CD20 (×100, original magnification). **(C)** The lymph node was formed by germinal centres immunochemically positive for Bcl6 (×100, original magnification). **(D)** The germinal centres contained small atrophic follicular dendritic cells immunochemically positive for CD21 (×100, original magnification).

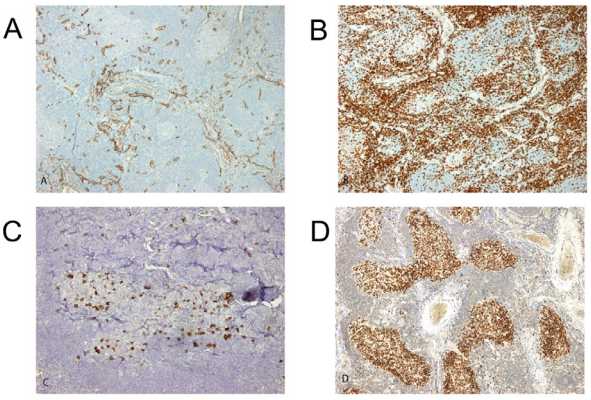

Figure 4. Further histological findings and their immunochemistry examination. (A) Blood vessels between the follicles immunochemically positive for CD34 (×100, original magnification). **(B)** Small lymphocytes immunochemically positive for CD3 (×100, original magnification). **(C)** plasma cells immunochemically positive for CD138 (×200, original magnification). **(D)** Ki67 staining ratio (x100, original magnification).

mass. Microscopic examination showed an organized lymphoid tissue consistent with a lymph node (Figure 3A), characterised by enlarged follicular structures

(CD20+; CD1-) (Figure 3B) formed by germinal centres (Bcl6+; Bcl2-) (Figure 3C) containing small atrophic follicular dendritic cells (CD21+) (Figure 3D), which were sometimes of large size and bizarre shape, and surrounded by a normal mantle zone.

Hyalinized small blood vessels penetrated the follicular germinal centres perpendicularly. Between the follicles there were numerous vascular structures (CD34+) (Figure 4A), small T-lymphocytes (CD3+) (Figure 4B) and few plasma cells (CD138+) (Figure 4C). No immunoreactive cells for HHV8 or CD30 were detected. The Ki67 proliferative index was very high (90%) (Figure 4D). The histopathological findings were consistent with Unicentric Castleman's disease, hyaline vascular type, with the presence of giant follicular dendritic cells.

3. Discussion

Castleman's disease (CD) is a rare benign lymphoepithelial disorder that usually occurs in the mediastinum as a nodal mass (*22*) but there have been reports describing extramediastinal lymph node enlargements (*3*). CD may be asymptomatic, as it often occurs in case of the hyaline vascular variant, or symptomatic, with diffuse lymphadenopathy and severe systemic symptoms, such in the plasma cell variant (*23*). The aetiology of CD is not completely clear yet: clinical evidences include chronic antigenic stimulation by a virus (human herpes virus 8 or Kaposi sarcoma-associated herpes virus) (*13,14*), chronic inflammation (*1*), immunodeficient state (*24*) and autoimmunity (*25,26*).

Furthermore, excess production of interleukin-6 (IL-6) plays an important role in the pathogenesis of the CD (*27*). Giant lymph node hyperplasia is generally treated with surgery (*28*).

According to the latest investigations, complete resections provide the same surgical results in deep and superficial CD (*29*). No recurrences have been reported in the literature after complete resection of the hyaline vascular type. Cytoreduction with radiotherapy and a combination of chemotherapies have been recommended in cases where complete resection is not achievable (*30,31*), such as the multicentric forms. The prognosis and outcome of the multicentric type are usually poorer due to many factors, like progression rate, infections and comorbidities (*32-34*).

Fine Needle Cytology (FNC) is a quick, cost-effective and safe diagnostic tool, which can be particularly advantageous in non-surgical diseases and has proved very useful for the discrimination between reactive lymphadenopathies and other malignant conditions. The use of FNA has led to a wide knowledge of the cytology of reactive lymph nodes, including the rarest conditions (*16-18*). However, FNA remains rather underutilized for the evaluation of lymphadenopathy, partially due to the lack of available expertise for the performance and interpretation of such samples (*21*). Several authors have emphasised the diagnostic importance of FNC in CD (*35,36*). Although only case reports are available in the literature, attempts have been made to describe the cytomorphological findings in CD (*37-42*) which can be indicative enough for it to be considered preoperatively, among other entities.

In our report the cytological picture was represented by lymphoid cells in different maturation stages, of both B- and T-cell type, and numerous atypical lymphoid cells varying from medium to large-size, similar to those reported by Hidvegi (*37*) and Cangiarella (*38*).

Mallik (*43*) suggested that the main and most consistent clue to the cytological diagnosis of CD is "the presence of large atypical cells with "crumpled tissue paper" like chromatin, occasional multinucleation, nuclear indentations and nuclear grooves". In our case the only characteristic that could be appreciated was the occasional multinucleation, whereas the atypical cells had scant cytoplasm, a single large, sometimes nucleolated vesicular nucleus with homogeneously scattered heterochromatin. Only few atypical cells with prominent nucleolus mimicking Hodgkin's cells, as commented by Mallik (*43*), were present in our samples, which did not show any expression of CD30. Hidvegi and his collaborators in the first FNA case report of CD (*37*) described the presence of capillary vessels in their aspirate. We also found capillary fragments in our case, which posed CD among the possible diseases. When the cytological features suggest this entity, imaging data and immunochemistry may play an important role in the final diagnosis. A hypoechogenic and hypervascular mass showing well-defined margins on imaging, with or without systemic symptoms, should include CD in the differential diagnosis. A polymorphic B-cell population (CD20+) with normal T cells (CD3+) and CD30 negative large atypical mononuclear, binucleated or multinucleated cells excludes the diagnosis of Hodgkin's lymphoma and thymoma. The observation, in such clinical setting, of large mono- bi- or multinucleated atypical cells with vesicular, nucleolated nuclei which do not display any reactivity for CD30, should raise the possibility of CD. In our case, the histological examination combined with immunohistochemistry gave the final confirmation of CD.

In conclusion, although it is probably not possible to give a definitive diagnosis of CD on FNC samples, the presence of branching hyaline capillaries penetrating reactive follicular germinal centres should at least raise this diagnostic possibility. After exclusion of other lymphoproliferative disorders, a careful review of the cytomorphology and clinical features should be carried out. Given the cytomorphological overlap and atypia in some cases, ancillary studies and/or excisional biopsy should be recommended and Castleman's disease can be suggested to the surgeon as a diagnostic possibility.

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Supplemental Figures

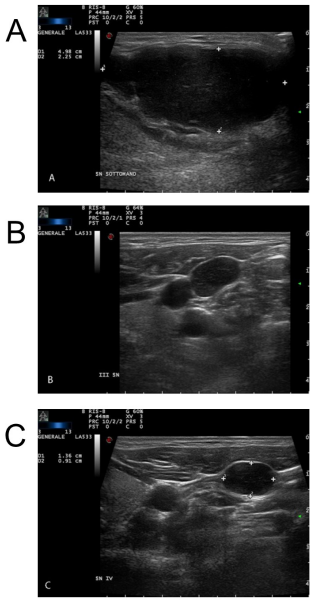

Figure S1. Ultrasound images of the nodules. (A) Ultrasound examination of the left submandibular area showing a major hypoechogenic mass with regular margins and light internal lobulations. **(B)** Normal appearing lymph nodes between Level III and **(C)** Level IV of the neck.

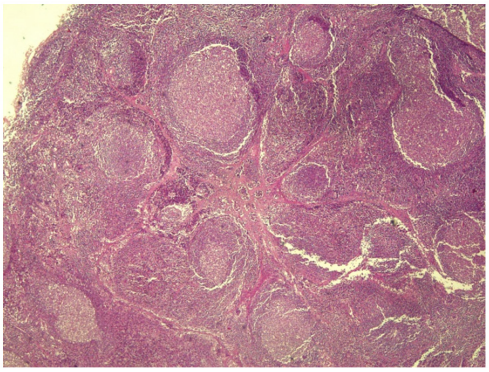

Figure S2. Histological findings. Structure of the lymph node of the II left submandibular Level formed by germinal centres surrounded by thick mantle zones (HE, ×40, original magnification).