Castleman's disease with diffuse cervical localisation: case report

Malattia di Castleman a localizzazione cervicale diffusa

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Key words

Lymph node hyperplasia • Castleman's disease • Diagnosis • Treatment

Parole chiave

Iperplasia linfonodale • Malattia di Castleman • Diagnosi • Trattamento

Summary

Castleman's disease is a rare disorder of the lymphoid tissue with a predominantly mediastinic localisation, but possible in any lymph node or extra-lymph node site. The aetiopathogenesis remains to be defined and, in the literature, only just over 500 cases have been reported, with only 57 located in a cervical site. Clinically, a solitary or localised form and a systemic or multicentric form can be distinguished, whilst, from a histological viewpoint, this lesion may be of the hyaline vascular or plasma-cellular type. Even if all the cases localised in a cervical site have been described as a single mass, the case described herein refers to diffuse cervical lymph-node hyperplasia with histological characteristics of the hyaline-vascular type, with the presence of a plasmacellular component. Evolution, over the 7 years following diagnosis, was benign, despite the fact that the patient was not submitted to surgical treatment. The low titre of B and T4 lymphocytes would appear to indicate that Castleman's disease might be an immunological disorder, due to atypical hyperplasia of the lymphoid tissue. It is suggested that Castleman's disease, in the cervical site, be classified into two subtypes: a cervical form, presenting as a single mass, and a multicentric cervical form. Data from a review of the literature are discussed.

Riassunto

La malattia di Castleman è un raro disordine del tessuto linfoide a prevalente localizzazione mediastinica, ma possibile in qualsiasi sede linfonodale ed extralinfonodale. L'eziopatogenesi è sconosciuta e in letteratura sono stati descritti poche centinaia di casi di cui solo 57 a livello cervicale. Clinicamente si distinguono una forma solitaria o localizzata ed una forma sistemica o multicentrica e, dal punto di vista istologico, un tipo ialino-vascolare e un tipo plasmacellulare. La diagnosi di certezza è possibile solo con l'esame istologico. Sebbene tutti i casi a sede cervicale siano stati descritti come una massa unica, noi abbiamo riscontrato un caso con linfoadenomegalie cervicali diffuse, a varietà istologica ialino-vascolare con discreta componente plasmacellulare. Questo caso ha avuto un'evoluzione benigna a distanza di 7 anni dalla diagnosi, nonostante la mancanza di un trattamento chirurgico. Un basso titolo di linfociti B e T4 farebbe supporre che la malattia di Castleman possa costituire un disordine immunologico, da riferire ad una iperplasia atipica del tessuto linfoide. Si propone una classificazione della malattia di Castleman localizzata a livello cervicale in 2 sottotipi: una forma cervicale a massa unica e una forma cervicale multicentrica. Una review della letteratura è discussa.

Introduction

Castleman's disease (CD) is a rare lymphoproliferative disease which usually manifests as an isolated form limited to the mediastinum, but may be localised at any level of the lymph nodes and other extra-lymph node areas. The aetiology and pathogenesis remain to be defined. From a macroscopic viewpoint, CD is characterised by a solitary or isolated form and a systemic or diffuse form. The 57 cases with a cervical localisation described in the literature, all belong to the isolated form. Histologically, a hyaline-vascular form may be more frequently observed and a plasmacellular form which occurs in only 10% of cases. Definitive diagnosis is possible only following histological examinations.

Case report

In June 1995, a 13-year-old female came to our attention with slow-growing bilateral latero-cervical lymphadenopathy, which the patient had discovered a few years earlier. The patient, who presented no symptoms and was in good general health, had previously been submitted to cycles of antibiotic therapy, which did not lead to any change in the volume of the mass.
Medical history, in family members, revealed 2 cases of long-standing aspecific lymphadenopathy, in a brother and in the father, at ascellar and inguinal level, respectively, which had resolved spontaneously.
Clinical examination of the neck revealed, upon hospitalisation, a "*proconsolare* appearance" with bilat-

eral lymph node masses at all levels of Robins, which were not painful, maximum size being 4 cm, with a smooth surface, parenchymatous consistency, and not fixed on the superficial and deep layers (Fig. 1).
The patient was submitted to routine haematochemical and serological examinations, chest X-ray and orthopantography, all of which were within normal limits. Immuno-serological assessments revealed only an alteration in lymphocyte typing, with monoclonal antibodies showing a reduced rate of B (CD19) lymphocytes (5.0%) and T4 (CD4) helper (33.9%) and a helper/suppressor ratio below the normal values. On the other hand, T3 lymphocytes (CD19) and T8 suppressor (CD8) were normal, being 69.4% and 28.2%, respectively. Assessments to detect anti-nuclear antibodies (ANA), anti-DNA antibodies, anti-ENA antibodies, circulating immunocomplexes and anti-cytoplasm antibodies of neutrophils were negative.
Ultrasound (US) examination confirmed the presence of bilateral latero-cervical lymph node clusters which were not evident at mediastinic, ascellar, abdominal or inguinal level.
The patient was submitted to explorative cervicotomy with removal of a medium latero-cervical lymph node on the left side. Histological examination revealed a case of CD of the hyaline-vascular type with a discrete plasmocyte component (Fig. 2).
Other investigations included:

– Computed tomography (CT) of the neck, with and without contrast medium, which confirmed the presence of diffuse bilateral latero-cervical lymph-adenopathy from the corner of the mandible to the mediastinum, showing a trend to conglomeration and signs of colliquation. Atypical impregnation of contrast is characteristic of these vascular forms (compatible with clinical aspects of CD).
– CT of the chest, with and without contrast, which revealed, in correspondence to the anterior mediastinum and in the prevascular site, the presence of a retro-sternal hypodense tissue probably of thymus origin, compatible with the age of the patient. There was no evidence of para-tracheobronchial or ascellar adenopathy.
– CT of the abdomen, with and without contrast, which did not detect subdiaphragmatic adenopathy or parenchymal alterations at liver, spleen, kidney or pancreas level.

Over the next 7 years, the patient, monitored at yearly intervals, showed a slow gradual improvement in the objective and US pattern of the lymphadenopathy which was slightly reduced in size at each examination (Fig. 3), with confirmation of the low titres of B and T4-helper lymphocytes.

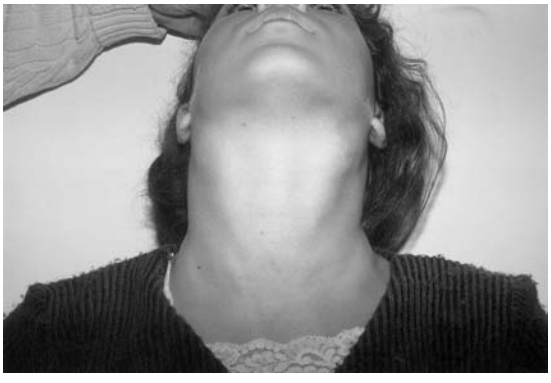

Fig. 1. Proconsular appearance of patient's neck at first observation.

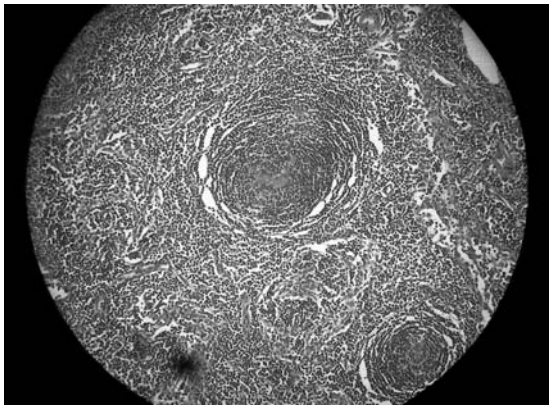

Fig. 2. Hyaline-vascular type with a discrete plasmocyte component.

Review

CD was first described by Castleman in 1954 [1] as a benign lymph node neoformation located in the mediastinum; two years later, Castleman [2] described the condition *as localised timoma-like lymph node hyperplasia.*
Since then, it has been variously defined as angiolymphoid hamartoma, angio-follicular hyperplasia, giant lymph node hyperplasia, follicular lymphoreticuloma, giant benign lymphoma [2-4], but "Castleman's disease" still remains the most valid definition since other definitions could give rise to confusion with a neoplasia or a hamartoma.
CD is a rare disease and, since the first report, only just over 500 cases have been observed [4], of which 57 localised at cervical level. Due to the occurrence of asymptomatic forms, it is difficult to estimate the ex-

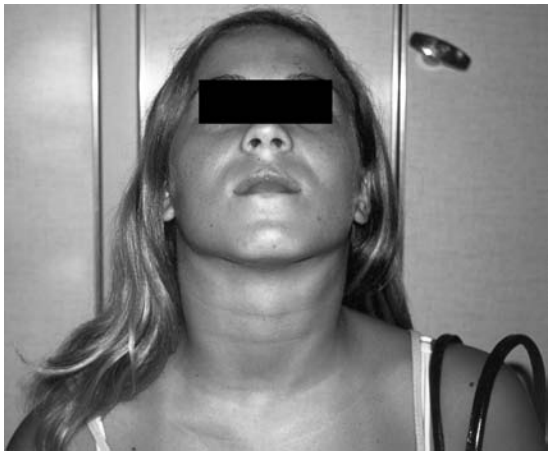

Fig. 3. Reduction of neck masses after 7 years.

act frequency.
CD occurs primarily in white and coloured individuals, as well as subjects of Mongolian origin; both sexes are equally affected; age at onset varies between 6 weeks and 76 years of age, with a peak incidence in the 2nd-3rd decade.
Histologically, there are two types: the hyaline-vascular or angio-follicular type, which is more frequent (90% of cases) and the *plasmacellular type* (10% of cases). A *mixed* or *transitional* form has also been described, but this is more rare [5].
The *hyaline-vascular* type is characterised by somewhat evident lymphatic follicles and by the hyaline-vascular proliferation of the germinative centres. These follicles seem to be surrounded by concentric layers of small mantellar lymphocytes with an "onion skin" appearance [6 7]. The interfollicular stroma is prevalent, with numerous post-capillary venules, rich in plasma-cellular formations, eosinophils, immunoblasts and plasmocytoid monocytes. There is also the "lymphoid subtype", variant in which a discrete expansion of the mantellar zone is evident, with germinative centres.
The *plasmacellular* type is characterised by dense interfollicular plasmocytosis. The follicles are similar to those of a normal lymph node, but the centre is completely lacking in hyaline-vascular proliferation.
The *transitional* or *mixed* form is less frequent and presents plasmocytosis with Hassal pseudocorpuscles [6].
Clinically, CD usually manifests with lympho-adenomegaly [7] involving the superficial and deep lymph nodes but it may be localised, in any extra-lymph node site and is found in an isolated or solitary form, in approximately 90% of cases, or in a systemic or multicentric form, in 10% of cases.

Systemic symptoms are rare in the isolated form and frequent in the multicentric form [3], thus suggesting that the number of lymph node areas involved may determine the severity of the symptoms.
Isolated CD is localised in the mediastinum in more than 70% of cases, from which it rarely extends to cervical level [2]. Cervical lymph nodes are the second most frequent site, involving 15-20% of cases [8], usually in a medium-high jugular site and beyond the carotid sheath.
In the head-neck district, the solitary form has been observed also at parotid, laryngeal, rhino-pharyngeal and retro-pharyngeal level.
Other localisations are: lung, ascellar, retro-peritoneal, pelvic, pancreatic, vulvar, renal hilus, skeletal muscles and connective tissue. In the extra-lymph-node sites, ectopic lymph-node tissues have been hypothesised as the origin [9].
The presence of the swelling may lead to compression of the respiratory airways, of peripheral nerves, of the biliary or urinary tract.
Thus, manifestations may occur, at a distance, such as glomerular nephropathies, myasthenia gravis, failure to thrive, peripheral neuropathies, medullar plasmocytosis.
The solitary form is histologically of the hyaline-vascular type in more than 90% of cases and, at times, is associated, in the plasma-cellular forms, with symptoms/signs such as anaemia, fever, perspiration, splenomegaly, and an increase in erythrosedimentation rate (ESR), leukocytosis, thrombocytosis, hypofibrinogenaemia, hypotransferrinaemia, increase in alkaline phosphatase, hyper-gammaglobulinaemia (particularly IgM), hypoalbuminaemia [9].
The *multicentric* or *diffuse* form, first described in 1978 [10], is, from a histological point of view, almost exclusively of the plasma-cellular type [10 11]. This is a systemic disease characterised by generalised lymphadenopathy involvement, including also the spleen, by systemic symptoms and different clinical conditions such as, for example, rheumatoid arthritis, AIDS, nodal or diffuse Kaposi syndrome, non-Hodgkin lymphoma, thyroidal amyloidosis, kidney failure, thrombocytopenic thrombotic porpora, xanthomatous and vasculitic skin manifestations.
This would appear to suggest that multicentric CD is a different disorder from the localised form and may evolve into a lympho-proliferative clonal disease. As far as concerns this disease, two types have been described: one with a better prognosis which involves only supra-diaphragmatic lymph nodes; the other, generalised, which is more severe on account of frequent sepsis.
Macroscopically, the masses usually present as a spheric or oval form, hard, well circumscribed, of a whitish colour, at times with haemorrhagic areas [4]. These may reach a large size (from 1.5 to 16 cm), particularly in

the deep localisations which become symptomatic later and do not usually invade adjacent structures [4].
The pathogenesis still remains to be elucidated, however, various hypotheses have been advanced:

1. *Inflammatory-infectious* This is the most likely hypothesis and the disease is held to be secondary to long-standing infectious stimulae. In fact, in the neck-facial localisations, the frequency of the rhino-pharyngeal infections would support the inflammatory-infectious theory.
2. *Hamartomatous or dysembryogenetic* The findings in favour of this theory are the absence of lymphatic sinuses, the rich and atypical vascularisation, the possible extra-lymph node localisation of CD and the lack of recurrence. Findings against are: the fact that the lesion is not congenital, that, apparently, it does not show familiarity and that the immunological disorders disappear after exeresis [5].
3. *Neoplastic* This has been abandoned since the disease has a benign evolution with rare recurrences [5].
4. *Immunological* According to some Authors, CD may be due to an immunological disorder, possibly at B lymphocyte level [12 13].

The diagnosis cannot be made only on the basis of clinical data or biological examinations.
CT of the district involved may be helpful since uptake of the contrast medium, by the mass, is uniform; the hyaline-vascular variety takes up more contrast medium due to the greater vascularisation [4], and, in 10% of cases, may reveal calcification.
NMR reveals neck masses with a low intensity signal in weighted T1 scans and increased intensity of the signal in weighted T2 scans, without, however, specificity elements [14 15].
Angiography reveals only the hypervascular pattern of the lesions and also the *fine-needle aspiration* does not lead to pre-operative diagnosis; only *histology* and post-operative *progression* allow a definitive diagnosis to be made.
Once a diagnosis of CD has been reached, attempts should be made to detect other sites involved.

Differential diagnosis

Due to its rarity and polymorphism, CD is rarely diagnosed early, and may give rise to problems of differential diagnosis with infectious adenopathy, particularly tubercular forms, lymphoma and neoplasia [14]. In a mediastinic localisation, it should be differentiated from timoma, teratoma, dermoid or bronchogeneous cysts. Histological findings are not easy to define since it is necessary to differentiate the disease from follicular lymphoma and from immune adenopathy, in particular "angioimmunoblastic lymphadenopathy".
Treatment, in the *localised form*, is exclusively surgical, also at cervical level. In the majority of the isolated forms, the lesion is capsulated, easily clivabile and excised, with a favourable evolution in the large majority of cases [16]; recurrence is rare and may be caused by incomplete surgical exeresis requiring another operation [10]. Very occasionally, the lesion cannot be removed and then the proposed treatment will be radiotherapy, which, however, has been found to be of little effect, even if, in a few cases, a favourable outcome has been achieved.
In the *multicentric forms*, few data are available concerning suitable treatment. Evaluation of the most suitable treatment is difficult on account of the variable course of the disease, which, even if often fatal, may occasionally regress spontaneously. Complete remission of the disease has been obtained with high doses of corticosteroids and immunosuppressive drugs [14], without surgical treatment. Chemotherapy, in association with steroids or with combinations used in the treatment of lymphoma, has led to successful results in a large number of cases. Even if radiotherapy led to complete recovery, in one case, in others no response whatsoever was achieved. Immunomodulators such as alpha-interferon have been used with transient success.

Prognosis

Prognosis differs depending not only upon whether the form is localised or multicentric but also upon the histological type.
Localised CD of the hyaline-vascular type is benign or, in a very few rare cases, locally malignant (the plasmacellular variant reaches a 9% malignancy rate [17]). Surgical exeresis, of the solitary form at cervical level, is both diagnostic and therapeutic, with good control in almost 100% of the hyaline-vascular types. On the other hand, the only description of the plasmacellular variety, in the neck, resulted in post-operative recurrence [18].
The *multicentric form*, instead, has a somewhat unfavourable long-term prognosis. In fact, the disease tends to persist for months or years with an often fatal outcome due to infectious complications which may be associated. Furthermore, in approximately 1/3 of the cases, evolution is of the neoplastic type towards a Kaposi sarcoma, large cell lymphomas, plasmocytomas or Hodgkin disease, with unfavourable prognosis, despite treatment [10].

Discussion and conclusions

The clinical case under discussion leads to a series of questions:

1. Is there familiarity?
2. Is this case a localised or multicentric form? And, if it is a multicentric form, why does it not have

an unfavourable prognosis, but is benign even without treatment?
3. What is the meaning of the finding of low levels of B and T4-helper lymphocytes?
4. Is this a histological hyaline-vascular or transitional, form?

Our considerations, in the light of data found in the literature, are as follows:

1. Familiarity in CD cannot be demonstrated with certainty, in our case, and has not been previously described.
2. A few rare cases of CD have been reported in the literature with a cervical localisation, all of which of the solitary type. To our knowledge, this would appear to be the only case of CD with a multiple cervical site, whereas cases in which, besides the neck, also mediastinic and abdominal lymph nodes are both involved, are more numerous.
   The benign course, in the absence of treatment, appears to suggest that this is not a diffuse form, but rather a particular type of the localised form with a multiple site. Thus, classification of a subgroup is proposed of the localised form with a cervical site: a cervical form with a single mass and a cervical multicentric form.
3. The finding of low levels of B and T4-helper lymphocytes would appear to confirm the hypothesis advanced by Komatsu et al. in 1996[13], that the disease would be caused by an immunological anomaly of B lymphocytes, to be considered as an atypical hyperplasia of the lymphoid tissue.
4. From a histological point of view, 96% of the cases of cervical CD described in the literature are of the hyaline-vascular type, and only one case of the plasmacellular type [8] and one transitional [13].

Since the case described here as of "the hyaline-vascular type with the presence of a plasmacellular component", uncertainty remains as to whether this should be classified as a hyaline-vascular type or a mixed type.

We decided not to submit the patient to further treatment, on account of the spontaneous benign course of the disease, after more than 7 years since the first observation.

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