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CASTLEMAN'S LYMPHOADENOPATHY: TWENTY YEARS OF OBSERVATION. I. GENERAL CONSIDERATIONS. MONOADENOPATHIC VARIETY

UN VENTENNIO DI OSSERVAZIONI SULLA LINFOPATIA DI CASTLEMAN. I. CONSIDERAZIONI GENERALI. LA FORMA MONOSTAZIONALE

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After a short review of the nosologic definition of Castleman's lymphadenopathy in its monoadenopathic form, the Authors describe five cases of this rare condition of lymphatic tissues, personally observed over a period of 17 years. The Authors try to evaluate the different pathogenetic hypotheses proposed in the last years. In their opinion the process falls into the group of autonomous proliferations. A subsequent paper will treat the systemic form of Castleman's lymphadenopathy.

KEY WORDS: Monoadenopathic angiofollicular hyperplasia of lymphnodes, angiomatous lymphoid hamartoma, venulo-capillary hyperplasia, hyaline vascular variety.

For several decades, literature concerning the pathology of lymphatic tissue has been enriched by a rare and singular nosographic entity which, for simplicity, we will desiginate « Castleman's lymphadenopathy ».

However, in the 60 years that it has been studied, numerous interpretations of its etiopathogenesis have arisen fostering an equally varied terminology. These various designations are listed and subdivided into four groups, each corresponding to a particular etiopathogenetic interpretation (Table I).

As is well known [3 10 16 31], the disease is defined histologically by the following elements: 1) follicular hyperplasia, with an increase of

TABLE I.

Historical evolution of the concept of «Castleman's Lymphadenopathy» according to its various designations.

Evoluzione storica del concetto di linfopatia di Castleman e denominazioni pertinenti.

Possible etiopathological interpretation	Designation	Author, year
I - Histogenetic association with hemolymph nodes	1) Primary hemangiolymphoma of the hemal nodes	Symmers, 1921 [28]
	2) Enlargement of hemal nodes	Lederer, 1923 [18]
	3) Giant hemolymph node	Pemberton et al., 1950 [27] Grimes, 1956 [12]
II - Histogenetic association with thymus, particularly Hassall's corpuscles (inclusion in thymoma group)	4) Benign thymoma	Patterson and Heller, 1943 [26] Thorburn et al., 1952 [30] Crane and Carrigan, 1953 [8]
III - Lymph node origin. Only superficially resembling thymus. Hyperplastic inflammatory nature	5) Localized mediastinal lymph node hyperplasia (resembling thymoma)	Castleman et al., 1956 [3] Katz and Dziadiw, 1960 [15] Chipman and Dolan, 1961 [4] Bersack and Howe, 1963 [2]
	6) Mediastinal angiofollicular lymph node hyperplasia (resembling thymoma)	Harrison and Bernatz, 1963 [13] Veneziale et al., 1964 [32]
	7) Angiofollicular lymph node hyperplasia	Talamazzi and Ravasi, 1965 [29]
	8) Giant lymph node hyperplasia	Keller et al., 1972 [16]
IV - Autonomous lymphoid proliferation resembling that of hamartoma or benign tumor	9) Lymph nodal hamartoma	Abell. 1957 [1]
	10) Follicular lymphoreticuloma	Zettergren, 1961 [34]
	11) Benign lymphoid masses of probable hamartomatous nature	Lattes and Pachter, 1962 [17]
	12) Intrathoracic lymphoid hamartoma	Hirst and Williams, 1964 [14]
	13) Angiomatous lymphoid hamartoma	Tung and Mc Cormack, 1967 [31]

follicles in number rather than in size; some of the follicles being characteristically « primary » i.e., lacking germinal centers; 2) characteristic structural alterations of all or the greater part of these follicles; 3) extensive hyperplasia of the venulo-capillary network in the remaining areas.

Concerning the 2nd point, structural alterations of follicles are the following: a) stroma organized in concentric layers, so-called « onionskin » appearance, both in the germinal centers, where present, and in the lymphocyte mantle. Proceeding centrifugally the layers decrease in width: at the center of the follicle they frequently form sclero-hyaline whorls which gradually shade as they approach the periphery. This stromal organization seems, at least in part, to be connected with the peculiar type of follicular vascularization; b) this vascularization is characterized by the radial direction of both afferent and efferent vessels, by an endothelial lining composed of tall endothelial cells similar to those found in postcapillary venules, and often by thickened and hyalinized vascular walls. Within the sclerohyaline formation, the capillary mass in the follicular center permits the emergence of a mesenchymal cell population considered by most to be endothelial but perhaps of another nature: adventitial?, dendritic?; c) relative depletion of the centroblastic/centrocytic line and the appearance of plasma cell aggregates of variable size in both the germinal center and the peripheral mantle.

With regard to point 3, venulo-capillary hyperplasia in the interfollicular spaces can mimic an angioma. The normal medullary architecture of the lymph node (cords and sinuses) is generally recognizable only in limited areas of the neoformation. The lymphatic parenchyma supported by this vascular network, is rich in plasma cells and immunoblasts and at times can even contain occasional polyploid elements vaguely resembling Sternberg cells. Macrophages and eosinophils are also present.

The histological picture just described, present in about 90% of cases, is, strictly speaking, the so-called « hyaline-vascular » variant of Castleman's lymphadenopathy [10 16].

Through a series of intermediate pictures in which the angiofollicular component decreases while the interstitial plasmacyte component increases, a much rare variant, the « plasma cell » type, is reached. In the very rare paradigmatic cases of this type, follicular morphology is nearly normal with a well developed centroblastic/centrocytic component in the germinal centers and possible macrophage reaction producing the « starry sky » pattern. Interfollicular spaces show a barely perceptible thickening of the venulo-capillary

network associated with a degree of plasmacyte hyperplasia bordering upon monomorphism[10 16].

Clinically, a wealth of literature has confirmed that the lesion is monocentric and benign in both its hyaline-vascular and plasma cell forms. Once surgically removed, recurrence is not described, as a rule. In the majority of cases, the only signs and symptoms are local, related to the presence of a mass which behaves like a benign tumor.

In a minority of cases, usually presenting with the plasma cell variant, in conjunction with the local phenomena, general signs and symptoms of inflammation are present: iron deficiency anemia, hypoalbuminemia, hyperα_2 globulinemia, polyclonal hypergammaglobulinemia with plasmacytosis of the bone marrow, elevated ESR, and at times lowgrade fever and sweats. These general phenomena usually regress definitively following surgical resection of the mass.

The thorax is the most frequent site of involvement. To date, the most complete review of this topic is the report of the combined study by the Massachussets General Hospital and the Armed Forces Institute of Pathology. They reported 81 cases, 74 of which were of the hyaline-vascular type and 7 of the plasma cell variant; 72 involved the thorax: 2 in the lung parenchyma, 5 in the right hilum, 9 in the left hilum, 25 in the antero-superior mediastinum, 15 in the posterior mediastinum, and 6 in other mediastinum sites. In the 9 remaining cases, the lesion was localized to various lymph node regions: cervical, axillary, retroperitoneal, pelvic. Cases have been reported in the literature in which the lesion was localized to areas which usually do not contain lymph nodes[6 17 34].

The nature and histogenesis of the process remain unclear. Presenting the various designations, we have listed four possible etiopathogenetic interpretations which appeared sequentially in time, with some overlapping. Amongst these we can immediately eliminate the one that establishes a connection between thymoma and Castleman's lymphadenopathy[8 26 30].

From one point of view, the question of whether or not the thymus represents the initial site of involvement of the disease in cases where the neoformation occupies the antero-superior mediastinum is valid. However, it is evident that early attempts to liken the follicles of this lymphadenopathy to Hassall's corpuscles were invalid since they were based on superficial analogies and did not take into account the epithelial nature of Hassall's corpuscles; not to mention that neoformation of these corpuscles is exceedingly rare in thymomas[20]. The other three etiopathogenetic interpretations will be discussed subsequently.

The aim of the present study, which will be dealt with in two papers, is to show that Castleman's lymphadenopathy, although relatively infrequent, is not as rare as believed, since we have diagnosed 10 cases in two centers serving the same region over a twenty year period. Of these, five were clinically in accordance with the classical description in the literature: monoadenopathic non-invasive, lack of general manifestations, and no recurrence after surgery. In Italian statistics, our patients can be added to the case described by Talamazzi and Ravasi [29] and to the three reported by Cozzuto and Torre [7].

TABLE II.

Castleman's Lymphadenopathy. Monoadenopathic form.

Linfopatia di Castleman. Forma monostazionale.

Case number (sex)	Age and year of onset	Localization (lymph node region)	Histological type	Therapy	Evolution of the disease Survival (mos.)
1-B.G. (M)	27 1959	retro-mandibular angle (right)	hyaline-vascular	surgery	CR-264
2-L.R. (M)	53 1970	Inguinal (left)	plasma cell	surgery	CR-132
3-B.D. (M)	52 1967	Scarpa's triangle (right)	hyaline-vascular	surgery (incomplete)	PR-90 (died of other causes)
4-P.P. (M)	33 1972	cervical (left)	hyaline-vascular	surgery + rad.	CR 120
5-S.G. (M)	45 1976	axillary (left)	plasma cell	surgery	CR-60

Our cases are described below. The second of our two papers will deal with a problem rarely treated in the literature, namely, the existence of a generalized form, both benign and not. The remaining 5 of our 10 cases, which we feel exemplify this multicentric condition, will be therein described.

Table II reports the data relevant to the 5 monoadenopathic cases.

As is evident from Table II, the histologic diagnoses were concentrated within a 17 year period, from 1959 to 1976. As of this writing, patient number 1 is alive and has been in good health for 22 years; number 2 for 11 years; number 4 for 9 years and number 5 for 5 years. Patient number 3 died 7 years after diagnosis of myocardial infarction; the inguinal-crural mass was only partially excised since it completely surrounded the large femoral vessels. All the patients were males. It is notable that in none of the 5 cases reported was the neoformation located in the thorax. As previously reported, in no cases were general manifestations seen clinically or evidenced by laboratory investigations.

Two cases, L.R. and S.G., presented a histological picture resembling the plasma cell type (Figs. 3, 4, 9, 10). In patient L.R. the follicles were partially hyaline-vascular (Fig. 3) while in patient S.G., there was extensive hyperplasia of the venulo-capillary network associated with plasmacytosis. The other three cases were clearly of the hyaline-vascular type (Figs. 1, 2, 5, 6, 7, 8). In one, B.G., there were no plasma cells but a few extrafollicular immunoblasts were seen and large, atypical mesenchymal cells were scattered in the follicular centers

Fig. 1.

Case 1. General view. Hyaline-vascular features of the follicles: some lackgerminal centers. HE 25×.

Caso 1. Veduta d'assieme. Aspetto jalino-vascolare dei follicoli, alcuni dei quali privi di centro germinativo HE 25×.

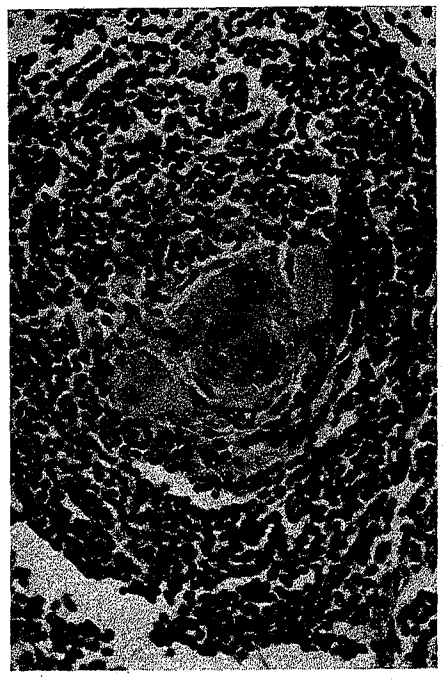

Fig. 2.

Case 1. A detail of a follicle. Sclero-hyalinosis of the follicular center with large, atypical mesenchymal cells. HE 250×.

Caso 1. Dettaglio di un follicolo: sclero-jalinosi del centro follicolare con grandi cellule mesenchimali atipiche. HE 250×.

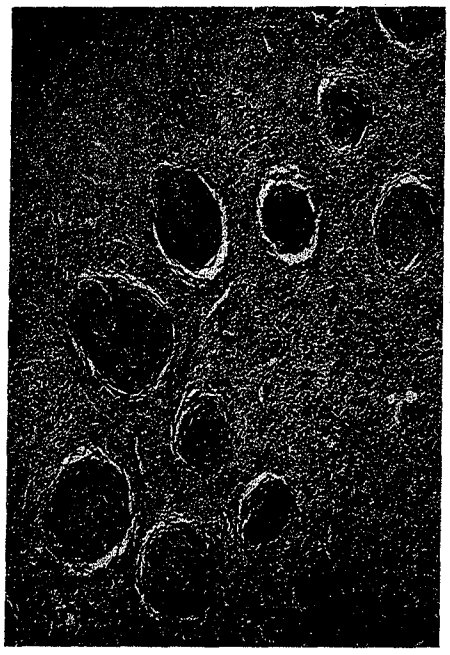

Fig. 3.

Case 2. General view. Onion skin-shaped follicular lymphocytic mantles. HE 25×.

Caso 2. Veduta d'assieme. Corone follicolari « a buccia di cipolla ». HE 25×.

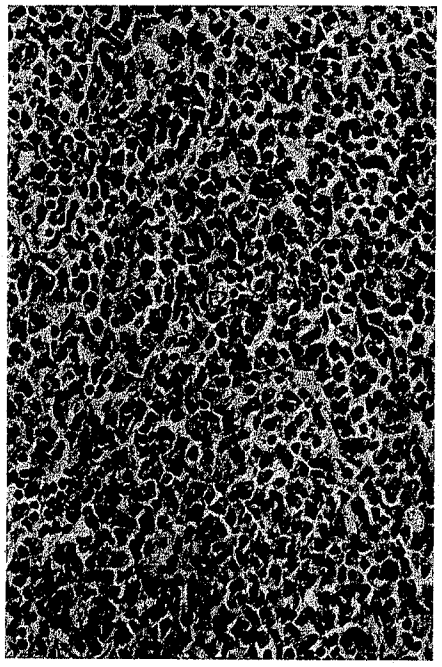

Fig. 4.

Case 2. A detail of an interfollicular zone. A carpet of plasma cells. HE 250×.

Caso 2. Dettaglio di una zona interfollicolare. Tappeto di plasmacellule. HE 250×.

Fig. 5.

Case 3. Typical hyaline-vascular aspect of a follicle. PAS 250×.

Caso 3. Tipico aspetto jalino-vascolare di un follicolo. PAS 250×.

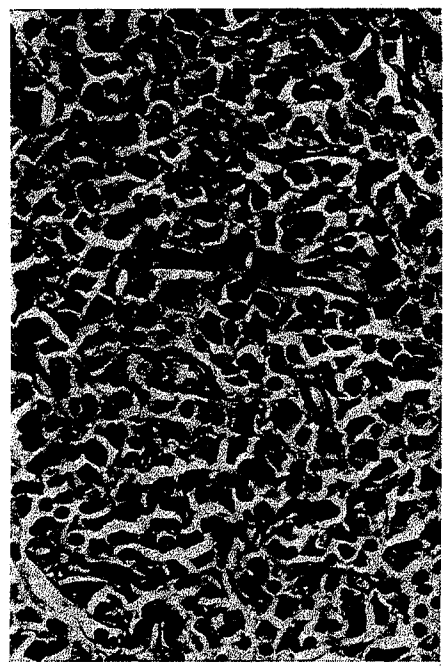

Fig. 6.

Case 3. Focal plasmocytosis in an interfollicular space, with venular hyperplasia. PAS 400×.

Caso 3. Focolaio di plasmocitosi in uno spazio interfollicolare con iperplasia della rete venulo-capillare. PAS 400×.

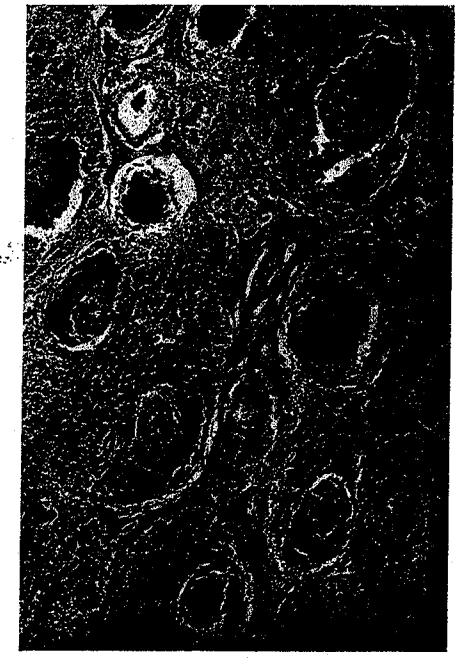

Fig. 7.

Case 4. General view. Numerous small follicles with interfollicular sclerosis. Lack of radial vessels. HE 25×.

Caso 4. Veduta d'assieme. Iperplasia follicolare in senso numerico con sclerosi interfollicolare. Assenza di vasi radiali. HE 25×.

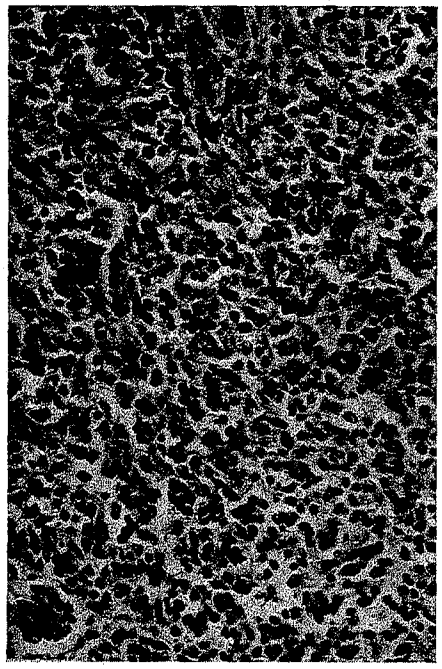

Fig. 8.

Case 4. Plasmacytosis and many vessels in an interfollicular space. HE 250×.

Caso 4. Iperplasia vascolare e plasmacitosi in uno spazio interfollicolare. HE 250×.

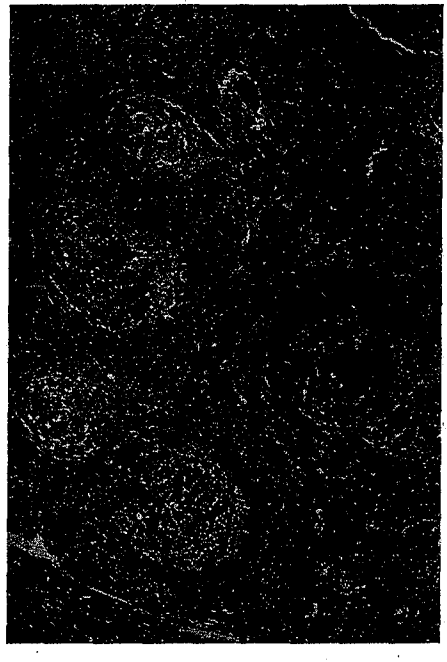

Fig. 9.

Case 5. Follicular hyperplasia. Attenuation of onion-skin appearance. HE 40×.

Caso 5. Iperplasia follicolare. Attenuazione dell'aspetto « a buccia di cipolla ». HE 40×.

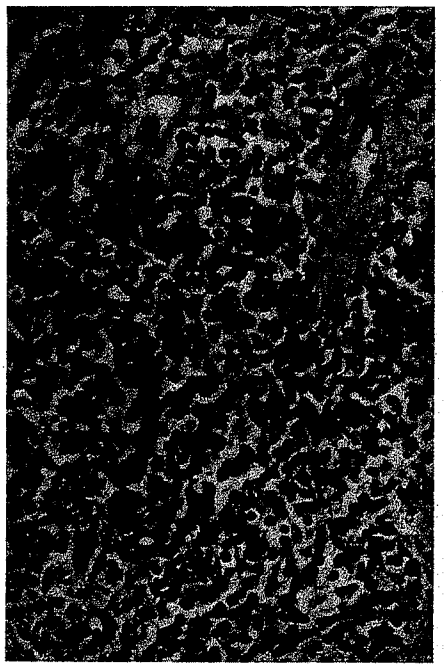

Fig. 10.

Case 5. An interfollicular space with a massive plasmocytosis. HE 250×.

Caso 5. Spazio interfolliculare con massiccia plasmocitosi. HE 250×.

(Fig. 2); In patient B.D., large foci of plasma cells were dispersed within the area of venulo-capillary proliferation (Fig. 6); the last case, P.P., showed intense interfollicular sclero-hyalinosis but radial vessels were absent from the follicles (Fig. 7).

Discussion

Until 2 years ago, Castleman's lymphadenopathy was described unequivocally by the following clinical profile: monoadenopathic localization, no recurrence after surgical ablation, absence of general manifestations, and, in the few cases where such manifestations are present, their definitive elimination following surgery. Our five cases fit into this profile.

Concerning the histogenesis of the disease, we have just eliminated the hypothesis of a relation to thymoma. To the arguments already proposed against such a hypothesis, we can now add the fact that, in a minority of cases reviewed in the literature and in all of our cases, the neoformation was not found intrathoracically but rather involved some lymph node region.

What can be said of the hypothesis, rather widespread since the early 1950's, regarding a histogenetic relationship to hemolymph nodes? [12 18 27 28]. Today, what value must be placed on Lederer's case [18] and on the two cases of Symmers [28] (one of which, moreover, was malignant and generalized) which conventionally are considered the beginning of the long bibliographic history of Castleman's lymphadenopathy?

Hemolymph nodes, according to anatomists working from the second half of the past century till the 1910's [5 11 21 22 24 33], were considered small, nodular lymphoid formations with a sinusoidal-type blood supply found physiologically on both sides of the axial skeleton and near the renal arteries in several orders of mammals, particularly in ungulates (pigs, oxen, sheep) and in primates (monkeys, man) [21].

All hemolymph node studies date back to the period just described; since then the study of these structures has been practically ignored. Reviewing the fundamental works written on this topic, which seem relatively accurate notwithstanding some notable differences in detail, convinces on of the actual existence of anatomical structures intermediate between a normal lymph node and a succenturiate spleen in ungulates and primates. But can such structures provide the anatomical basis for the development of Castleman's lymphadenopathy? Can this entity be considered a « giant hemolymph node? » [10 25].

Such a hypothesis could be supported by the predominantly axial (mediastinal, pelvic) location of this lymphopathy. Then, the occasional case where the process arises in a typically lymph nodal or any how peripheral site would imply the preexistence of ectopic hemolymph nodes, disontogenetic in origin. In our opinion however, two facts concerning morphology and structure constitute the strongest argument against such a histogenetic hypothesis. These are: 1) in Castleman's lymphadenopathy, the blood circulates within authentic vascular channels (arterioles, capillaries, venules) and not in sinusoids characteristic of hemolymph nodes. The sinusoids, where present, are residuals of pre-existent lymph nodal architecture and contain lymph; 2) there does not appear to be any relation between normal follicular morphology of the hemolymph nodes and the hyaline-vascular alterations of the follicles so frequent in Castleman's lymphadenopathy.

Neither do we advocate the hypothesis supported by many researchers [2 3 4 13 15 16 29 32], including Castleman himself [3 16], that the disease is the result of a reactive, inflammatory process. No known etiologic agent, no irritative process, no hetero- or autoantigenic stimulation is capable of evoking these characteristic histological chan-

ges in normal lymph nodes; this is especially true when one considers the hyaline-vascular type. Moreover, the growth of the neoformation is usually extremely slow and almost always asymptomatic except for eventual symptoms due to compression and obstruction.

The characteristics presently listed seem to affirm both a predominantly lymph nodal origin of the proliferation and the autonomous nature [1 9 14 17 31 34] of the process, autonomous meaning any tissue growth disconnected from functional regulatory mechanisms. Therefore a non-reactive growth be it classified as dysplasia, a dysontogenetic process, or frankly tumoral in nature. In particular, the neoplastic hypothesis could be supported by a couple of data provided by Fischer et al.[9] in 1970: 1) the presence of viral particles seen by electron microscopy; 2) malignant evolution of tissue explants grown in the maxillary pouch of the hamster. These data are extremely interesting even if they have not been confirmed (but these experiments have never been re-performed) since their original description.

In the second part of this study, we will return to the consideration of the hypothesis that Castleman's lymphadenopathy is an autonomous proliferative process of the lymph nodes.

RIASSUNTO

Dopo una breve esposizione della problematica relativa all'inquadramento nosografico della linfopatia di Castleman nella sua forma monoadenopatica, gli AA. effettuano una presentazione epicritica di cinque casi, da loro osservati nel corso di 17 anni, di questa rara affezione dei tessuti linfatici. Segue un tentativo di valutazione delle diverse ipotesi patogenetiche susseguitesi negli ultimi decenni. Gli AA. optano infine per l'inquadramento del processo nell'ambito delle proliferazioni autonome dei tessuti linfatici e preannunciano un successivo lavoro sulla forma sistemica della linfopatia di Castleman.

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