Review Article

Intravascular Lymphoma: A Heterogeneous Prognosis of Malignant Vasculitis

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Abstract

The objective of this review is to describe at the intersections of different specialties, Intravascular Lymphoma (IVL), a form of lymphoma of heterogeneous clinical presentation and difficult diagnosis, for which the chemotherapy treatment must be quickly discussed. There are many clinical forms of IVL, and the biopsy site must be quickly determined in particular through the PET scan. Prognosis is poor, but heterogeneous and predictive survival factors emerge. They exist B forms but also T and NK. The central nervous system impairment is bad prognosis. Treatment should be started as soon as possible after discussions with the hematologists. In B form, polychemotherapy containing Anthracycline, in combination with rituximab is probably the best choice.

The IVL should be better known to all and appeared to be a differential diagnosis of vasculitis. Therapeutic tools to prevent a relapse in the central nervous system must be developed. The presence of PD-L1 on these lymphoma cells must be confirmed to consider the anti-PD-L1 and anti-PD-1 antibodies in combination with multidrug therapy and anti CD20 on terms to be determined.

Keywords : Intravascular Lymphoma; Malignant Vasculitis; PET Scan; PD-L1; Rituximab

Introduction

IVL is a rare disease whose incidence and prevalence are unknown. Since 2001, according to the World Health Organization, it is a subtype of Large-B-cell lymphomas [1], although other forms have been described more recently. This lymphoma is defined by the proliferation of malignant lymphoma cells in the vessel lumen and particularly of small vessels [2-4]. As of early 80 successive descriptions with various names, have come to question the uniqueness of that entity: malignant angioendotheliomatosis, angiotrope lymphoma, hémangioendothéliose [5].

The first diagnosis was made during autopsies. These have helped to highlight lymphomatous proliferation in the blood vessels of multiple organs: heart, brain, liver, prostate, lung, pancreas, spleen, kidney, bone marrow, ovary, pancreas [6]. Because of the many potentially affected organs by this malignant intravascular proliferation, clinical forms are varied expressions, sometimes frustrated and therefore appeal to different specialists. The diagnosis is made by pathologic and immunophenotypic analysis of a biopsy of an affected organ.

There is no information on the pathophysiology of this disease, the reported clinical cases are scattered, with series about a few dozen patients. Until recently there was no study indicating potential predictors of survival for a disease whose evolution is, in most cases, quick and fatal, with few lasting re-mission after treatment and exceptional long-term survival without treatment for specific clinical forms [6].

This review aims to decline the different clinical forms of IVL in order to make a rapid diagnosis with a complete and accurate mapping of the disease. We will discuss the pathology elements, immunophenotyping and molecular biology which allow to refine the place of LIV in other lymphoma diseases. We will discuss the place of certain imaging tests such as MRI and PET scan in the study of the extension and monitoring of disease. Finally, we will discuss the prognosis and nature of treatment in which the monoclonal antibodies associated with multidrug therapy based Anthracyclines have a prominent place.

Clinical Forms

IVL is a very aggressive lymphoma, stage IV in the classification of Ann Arbor in 68% of cases and affecting the average person aged 70 years (34-90 years) [7]. At first glance,

there seems to be a noticeable difference between the case of LIV reported by Japanese teams ("Asian variant") and others. The first report in more than 2/3 of cases of hemophagoytic syndrome with fever, liver damage, spleen, bone marrow. Skin involvement is relatively rare. Evolution is rapidly unfavorable with a median survival of 2 to 8 months [8-10].

In other cases, the most expressive organs are the skin and the central nervous system. Cutaneous manifestations are rich and nonspecific: rash erythematous, indurated plaques, purple plates, appearance of orange skin, cellulite, tumor or nodule more or less ulcerated, telangiectasia. Their locations are varied. It can be a single lesion and skin involvement may be the only regained. Ferreri, et al. report this violation to be isolated in 10 patients of 38 of their series with a very special prognosis that they referred to as "Varying skin."

In the same study, one third of patients had Central Nervous System (CNS) impairment (5 of findings at autopsy) revealed by multiple manifestations: sensory or motor deficits, meningoradiculitis, paraesthesia, aphasia, dysarthria, hemiparesis, epilepsy, myoclonus, decreased transient vision, vertigo. These symptoms were isolated from 5 patients [7]. Renal involvement revealing the disease has been reported in 7 patients [11-16]. This was nephrotic syndrome with sometimes hematuria. Two reported cases where the diagnosis of temporal arteritis was raised on the hyperesthesia combination of scalp and inflammatory syndrome [16,17]. In one case the corticoresistance associated with a discrete renal failure and hematuria had revealed the diagnosis of IVL on pathological examination of renal biopsy. The hyperesthesia of the scalp was finally a sequel to an intervention on a meningioma [16]. It will be noted a reported case in which Horton disease diagnosis was evoked in a sharp and unilateral decrease in visual acuity associated with proptosis.

Achieving the hematopoietic organs was traditionally uncommon in the first reported cases. According to Ferreri, this remains true for glands (11%), but bone marrow involvement may affect one third of patients and is then associated with liver damage and spleen with the presence of thrombocytopenia. Bone marrow involvement is sometimes the only objective study and should be sought on the piece of bone marrow biopsy, especially when there is unexplained fever.

The presence of fever associated with cough and possibly dyspnea may be associated with pulmonary hypertension secondary to pulmonary multi-focal disease [18]. Pulmonary perfusion scintigraphy may point to known images in certain diseases of endothelium leading to pulmonary hypertension. In this case, in the absence of other call point, the diagnosis is very difficult and this has led some authors to propose, as an investigative tool, right catheterization cytoaspiration. Visible images on a CT scan are nonspecific with a thickening of the interlobular septum, or

bilateral diffuse ground glass attenuation in the whole lung. The endocrine disease may also lead to clinical expression depending on the degree of infiltration of the gland in question [19-21].

Other modes of revelations were reported: potentially sudden deafness secondary to a labyrinthine infarction [22], sudden bleeding gynecological origin in a postmenopausal woman who revealed a uterine tumor process [23], change in color and size of cutaneous hemangiomas known in connection with an infiltration of these hemangiomas by tumor cells [24], coma associated with hemolytic anemia [25], hypotension likely reached the autonomic nervous system [26], pancreatic mass tail with a post-mortem diagnosis [27], thickening of the bladder wall in a context of deterioration of the general condition and disorientation [28]. So completely original, IVL can be combined with other tumor events, at the same time or not. Some solid tumors, renal cell carcinoma, liver hemangiomas were found concomitantly [7,29].

Regarding hematological tumors, IVL was found associated with large B-cell lymphoma [2,30-32]. This particular coexistence lymphoma described in the CNS is by some authors mention the possibility of a continuum between these two pathological entities [33]. Other patients had in their history follicular lymphoma, chronic lymphocytic leukemia, an intragastric MALT lymphoma or large B cells lymphoma [32,34]. The extravascular infiltration therefore not exclude the IVL. Recently manner intravascular B lymphoma was described in the evolution of rheumatoid arthritis treated with methotrexate [35].

Biologically we insist on increasing the plasma LDH levels and beta-2 globulin, present in 90% of patients, associated with anemia in 2/3 patients. Depending on the organs affected, can be also documented impaired liver function tests [36-38], renal function or endocrine functions [39-41] and increased protein levels in CSF for infringement of advanced CNS impairment [2,3,42]. Malignant cells are rarely found in CSF. A significant increase in serum ferritin should suggest a hemophagocytic syndrome. Urinary sediment abnormalities, particularly if it is a more or less proteinuria associated with hematuria, suspecting an infiltration of intra-renal capillaries.

Pathology, Phenotyping and Molecular Biology

The diagnosis of IVL is affirmed by the presence of tumor cells, lymphomatous type within the capillaries of a given organ. Many organs may be involved. There is no tissue infiltration outside where another tumor disease infiltrates the same organ. To illustrate histological examination, we chose to describe renal impairment of Intravascular-B-lymphoma (IVBL)

The size of the glomeruli is increased due to the often massive infiltration by lymphoma cells. Glomerular capillaries are infiltrated by large cells, and the malignant character in the majority of cases of IVBL already described, expressing markers B. The

glomerular basement membrane is normal and malignant cells are also present in hair peritubular. The interstitial is not undercover. Immunohistochemistry revealed strong labeling with anti-CD20 antibody. T markers, CD22 and monocyte markers are negative. There is no expression of endothelial markers: CD34, CD31, or FVIII expression or Lambda Kappa chains. The mechanisms contributing to the presence of proteinuria is unknown.

The link between this lymphoproliferation and kidney disease is here entirely original. Usually this type of association described in other circumstances: exceptional primary lymphoma of the kidney with a massive infiltration of the renal parenchyma but where glomerular disease is rare, cases of Hodgkin disease associated with minimal glomerular lesions (10.4%), B lymphoproliferative syndromes associated with glomerular mono or polyclonal immunoglobulin deposition such as chronic lymphocytic leukemia and membranoproliferative glomerulonephritis or cryoglobulinemia.

The study immunophenotypic and molecular biology of IVL, was first reported par Yegappan during the study of 18 patients. Phenotypic heterogeneity is evident. At 8 men and 10 women the results were: CD20 + 94%, + bcl2 89%, CD5- and CD10- and bcl6- 56%, and CD10- CD5-: 61% CD5 + and CD10-: 16 %, CD5- and CD10 + 16%, + BCL6 and CD5 +: 17%.

In situ hybridization did not reveal the presence of EBV and study in PCR no translocation 14-18. Besides studying the rearrangement of heavy chain genes had documented a fragment of the same size for all suggestive of the same clone [43]. Some authors have identified 3 groups: CD5 + and CD5-CD10 +; CD5-CD10-; CD5 + CD10- with no difference in overall survival [44]. In 50% of cases of LIV, Cytogenetic abnormalities relate to chromosomes 1, 6 and 18 [45]. A double expression of MYC and BCL-2 has been described in a woman who presented with chronic pelvic pain associated with fever, and parts removed from hysterectomy, ovariectomy, salpingectomy helped to make the diagnosis [46].

Expression of BCL2 and MUM1 has been reported without clinical significance [47]. In a cohort of 25 patients among which 6 had a skin limited disease, a high prevalence of MYD88 L265P (44% of the patients) and CD79B Y196 (26% of the patients) mutations has been described [48]. About 20 cases of T phenotype IVL have been described in the literature. They preferentially occur in patients over the age of thirty, the CNS impairment is common and abdominal pain due to infiltration of the gut vessels. Evolution is quickly fatal [49]. Some cases of IVL NK phenotype were described: CD56 +, CD3 epsilon +, CD20-, CD4-, CD5-, CD8-. A 41-year-old patient had skin lesions of the extremities expressing EBV. He was in remission 1 year after chemotherapy and bone marrow transplant. A 47-year-old female patient showed a diffuse infiltration table and died quickly despite treatment initiation [50].

Imaging

Imaging tests are relatively ineffective in exploring IVL. Indeed, there is not a very significant increase in the size of the bodies involved in the intra-vascular proliferation, unless there is another associated tumor disease. Two examinations however deserve mention: brain MRI and PET scan.

There are no pathognomonic symptoms IVL visible on brain MRI. In addition, MRI does not detect lesions in half of patients with symptomatology suggestive of CNS. When present, the most frequently found lesions type are focal ischemia or hyperintense white matter and the main differential diagnosis are the vasculitis [51]. Just as lumbar puncture, brain MRI, however, is done routinely in the evaluation of the disease.

In the case of infiltration of other organs, the expected results of MRI are uncertain and unspecific. However, they can guide a biopsy. The PET scan whose marker is on 18-fluorodeoxyglucose has a particular interest in mapping and monitoring of Hodgkin lymphoma disease or not. In IVBL review helps guide diagnosis, guiding biopsy and map disease [52-55]. It's interest in monitoring the disease seems obvious but remains to be seen. In one reported case, severe hyperactivity was documented in the pulmonary territory, spleen and kidney in a patient for which renal infiltration was certain and probable lung. The PET scan was then repeated three times throughout evolution, and extinction of the activity was correlated with the disappearance of other activity indices, clinical and biological [16].

Prognosis and Treatment

The overall prognosis of LIV is rapidly unfavorable let alone if the diagnosis is difficult as an isolated fever, or if there is a hemophagocytic syndrome present in the foreground. Recently, some prognostic factors have been established to specify more favorable developments, in particular as regards the isolated cutaneous forms. In this review, we discuss the form of IVBL.

In 1989 Domizio reported a series of 47 patients treated with chemotherapy, including 5 who achieved complete remissions. In this study, the median survival was 5 months with a maximum of 24 months. There was no benefit of radiation therapy used on extravascular sites or CNS [56]. A review of the literature published by Di Giuseppe 5 years later, performed the analysis of the evolution of 35 patients. Remission was achieved in 29% of cases with a short follow-up (8.5 months). Forty-six percent of patients died because of the disease progression with a tracking 10.5 months. Five patients (26%) were alive and in remission with a median follow up of 69 months [6].

In cases where the kidney shape was in the foreground, 4 of the 6 patients treated with chemotherapy were in remission after chemotherapy and the other two died quickly in the first month. A seventh patient is in remission lasting more than two years after the end of therapy with CHOP and rituximab administered at high frequency [16]. Since 2000, and this was subsequently confirmed, the treatment keystone is combination chemotherapy containing at least anthracyclines [6,57,58]. In the series of Ferreri, where patients are treated with CHOP chemotherapy, survival at 3 years was 58%. However, there are other cases where, with the same protocol, many failures are reported, be they of a progression on therapy or a fatal relapse.

Therapeutic intensification with high-dose chemotherapy gets there also very mixed results with two pitfalls interlinked: the usual age of revelation of IVL (70 years on average) and the strong lethal toxicity of chemotherapy [38,59,60]. Ferreri, et al. have published a series of 38 patients who can approach prognostic factors and to isolate cutaneous they call «Varying skin.» Thirty patients were evaluable for their living. Twenty-two patients were treated with chemotherapy (19 with Anthracyclines and 3 by alkylating under a cutaneous form and two very elderly patients), 5 with surgery alone whose resection was total in 4, 1 by radiotherapy (cutaneous form), 1 by corticosteroid (multiple skin lesions) and one was not treated. Seventeen patients had an objective response (56%), among them 8 relapsed (47%). Nine patients progressed on treatment (30%), and 4 patients died due to the toxicity of the treatment (13%). Seventeen patients (43%) were therefore considered in check, and in the first year of monitoring. Of these seventeen patients, some of them received salvage treatment: radiotherapy skin: 1 (complete remission M167), intensification (MACOP-B and CHOEP) with autologous bone marrow transplantation for the purpose of consolidation: 2 (in complete remission at M19 and M71), intensification with autologous bone marrow transplantation at the time of systemic relapse: 2 (died due to the toxicity of the treatment). One patient had a spontaneous remission of his skin lesion. Overall survival at three years for the entire series was 25% (+/- 7%). The originality of this series is mainly due to the fact of having established prognostic factors in uni and multivariate analysis. Both tests can take as good prognostic factors: «variant skin» (p: 0.008), the «performance status»: 0-1 vs. 2-4 (p: 0.009), stage of the disease: 1 vs 4 (p: 0.02), treatment with chemotherapy (p: 0.04).

The «variant skin» was linked to sex as it was in 100% of cases in women. Two patients had a «Performance status» less than 1. Their average age was much lower than for other patients (59 years vs. 72). However, other signs of aggression were present in these skin types: advanced stage, LDH, B symptoms and anemia. In addition, this group of patients with cutaneous localization was uncoordinated development. Only patients with a single cutaneous location, treated locally had a long survival. Patients with multiple cutaneous lesions treated with chemotherapy met in 86% of cases, but with frequent relapses in the first year of monitoring.

More generally in the IVL, the staging problem and therefore of disease classification is in the foreground. As part of the validated tools for the staging of lymphoma, here it is impossible to know with certainty the reality of capillary infiltration of an organ. This, as might be sought on a scanner cannot be correlated with disease stage. In other words, a negative result does not necessarily mean a disease stage 1. The prognosis of this lymphoma is severe with late diagnosis in 1/4 of the cases did the autopsy, due to a rapidly unfavorable evolution leaves little time to diagnose. Patients with CNS impairment at diagnosis quickly relapse in the same site. Some authors report a survival of 12% at 2 years after the CNS relapse for patients who had no central nervous system impairment at diagnosis [61]. The risk of relapse in the CNS was not dependent on the use or not of the anti-CD20 antibody in addition to multidrug therapy.

A Canadian series of 29 patients reported an overall 3-year survival of 47%. 58% of patients died following a degradation of general status, pancytopenia or progression of neurological involvement. Although in this series 10 patients had received either methotrexate high dose or intrathecal. In the end all patients received multidrug therapy based Anthracyclines first intention and 53% of them reached complete remission [44]. Several observations are in line with a first CHOP regimen and anti CD20 [62-65]. Depending on the tolerance of the treatment, and the rapid evolution of the disease, can discuss both an increase in the frequency of treatments (every 15 days), and secondly an increase in dose chemotherapy, including those of alkylating and anthracyclines. In some cases, a therapeutic intensification followed by autologous bone marrow or stem cells can be proposed. The decision rests with hematologists and should meet the same criteria as for lymphoma B, namely the presence of at least two poor prognostic factors. If therapeutic intensification, the best prognosis is obtained for a disease that has responded well to treatment. Thereafter, the recent description of the expression of PD-L1 in tumor cells IVBL to be confirmed by other studies immunohistochemical and allows already to convene monoclonal anti PD1 and anti PD-L1 as a potential therapeutic tool in combination with a multidrug therapy with Anthracyclines and optionally also with anti CD20.

In the cohort of patients with MYD88 and CD79 mutations there was no influence disease-specific survival with a 3-year OS of 43%. Those patients did not receive any Rituximab and a majority only supportive care. The authors suggest a new therapeutic approach as well as in diffuse large B cell lymphoma in which those mutations are more sensitive to a Bruton Tyrosine Kinase inhibitor that block NFkB pathway [48].

Conclusion

IVL, by its very fragmented rendering within the body's capillaries is of interest to mainly internists. Diagnosis is difficult but must be early to avoid functional alterations of the tissues that complicate treatment. The role of the PET scan is central to establish the diagnosis, guide the biopsy, map the disease and probably follow the effectiveness of the treatment. The treatment must be started very quickly, in consultation with the hematologists.

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