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Case Report

Multiple Sclerosis and Subcutaneous Panniculitis-like T Cell Lymphoma with Hemophagocytic Syndrome: The Role of Treatment Sequencing in the Pathogenetic Mechanism

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Abstract: Introduction: Although panniculitis-like T cell lymphoma (SPTCL) and hemophagocytic syndrome (HSP) have been described as complications following immunosuppressive treatments, there are no reported cases of concomitant SPTCL/HSP and multiple sclerosis (MS). **Materials and Methods:** We describe the case of a patient affected by an aggressive phenotype of relapsing remitting MS, characterized by consecutive severe relapses with no complete remission. He developed panniculitis-like T cell lymphoma (SPTCL) and hemophagocytic syndrome (HSP) after receiving multiple immunosuppressive treatments in sequence. Despite the aggressive nature of these complications, the patient responded well to a combination of Gemcitabine and Cisplatin. **Discussion and Conclusions:** With this case, we suggest that physicians always consider blood diseases as possible MS therapy complications, especially in the sequencing setting, and also consider uncommon treatments in those with autoimmune predispositions.

Keywords: multiple sclerosis; disease-modifying therapy; panniculitis-like T cell lymphoma; hemophagocytic syndrome

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1. Introduction

Subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a rare cutaneous T cell lymphoma, which usually manifests with subcutaneous neoplastic CD8 T-cell infiltrates [1]. Although previously divided into two subtypes, the αβ T-cell phenotype (CD4−), with lesions confined to subcutaneous tissue, and γδ (CD4/CD8-, CD56+), with involvement of the dermis and epidermis and a poorer prognosis [2], now, the recent revision of the World Health Organization classification of lymphoid neoplasms considers only the αβ subtype as SPTCL [3].

Typically affecting individuals aged 30–35 [4], SPTCL can be associated with autoimmune diseases [5], and its pathogenetic mechanisms remain unclear. Recent studies have identified genetic mutations, such as HAVR2, and epigenetic changes in the PI3K pathway as potential causes, correlating with clinical severity and treatment responses [6,7].

About 15–20% of cases are complicated by hemophagocytic syndrome (HPS) [8], a rare, life-threatening state of aberrant activation of the CD8+ T-cells and cytokine release triggered by genetic mutations or infectious, inflammatory, and neoplastic conditions [9].

The case presented involves a patient with highly active relapsing remitting multiple sclerosis (RRMS) who, after extensive treatment with immunomodulators due to consecutive severe relapses with no complete remission, developed concomitant SPTCL and HPS. This situation could provide insights into the underlying mechanisms of these conditions and their potential connections.

2. Case Report

This is the case of a 45-year-old man who experienced a sudden loss of visual acuity to the left eye when he was 23 (2001). When he was referred to our MS center, we performed a viral panel (negative for any infections) and a brain MRI, which showed a high load of T2-FLAIR periventricular and subcortical white matter demyelinating lesions. At the clinical examination, visual acuity deficit and nystagmus were detected; therefore, clinical features, MRI findings, and remission after corticosteroids led us to diagnose RRMS with a retrobulbar optic neuritis (NORB) clinical onset, and treatment with Interferon beta 1a was started (12 MUI; three subcutaneous injections per week), given its indication as first-line in that form of MS.

After 1 year, he experienced again an NORB in the left eye, which recovered partially with steroid bolus; at clinical examination, the expanded disability status scale (EDSS) was 2.5, with the following functional status score (FSS): visual system 2 (left visual acuity 5/10) and brainstem 2.

While under interferon treatment, the patient experienced five further relapses.

That kind of progression led us to suspect a highly active form of RRMS, confirmed by the continuous clinical worsening experienced by the patient over the following 10 years.

Indeed, EDSS continued to worsen slowly, MRI brain lesion load increased, and, concomitantly, he started to complain of difficulties in walking more than 500 m; FS: visus = 2; brainstem = 2; ambulation = 2; EDSS: 4.

Therefore, in 2011, natalizumab, 300 mg every 4 weeks, was started (given its indication in patients with relapsing remitting MS with high activity), even though a switch to another therapy was proposed some relapses earlier.

We kept the patient on that medication for the following five years, with stable EDSS, no radiological activity at annual MRI, and always negative antibodies against the John Cunningham's virus (JCV) titer.

At the beginning of 2016, the patient experienced sudden right-side hemiparesis, which partially remitted with steroid bolus, and anti-natalizumab antibodies were detected. The new neurological examination revealed an EDSS = 5 (FS: visus = 2; brainstem = 2; ambulation = 3) and MRI showed new T2 lesions in the spinal cord.

Due to the new disability accumulation (ambulation from 2 to 3), the patient was then switched to alemtuzumab treatment, 12 mg/day, administered by intravenous infusion for 5 consecutive days in the first year and 3 days the following year. Despite clinical and MRI stability, after the second cycle, that drug led to Alopecia Universalis (AU), which he had already experienced in youth.

Moreover, after 1-year follow-up from the second alemtuzumab cycle, he was restarted on MS treatment because of new MRI brain lesions, and rituximab 1000 mg every 6 months was chosen after consultation with dermatological specialists, since it had been reported to be an option also in AU [10]. Nevertheless, after the second infusion of rituximab, he experienced a further clinical relapse, again characterized by an hemiparesis of the right side, associated with an enlargement of the brain lesions at the MRI. After recovery with steroid bolus, ocrelizumab was started following the classical scheme (600 mg divided into two intravenous infusions both of 300 mg within two weeks of each other), and 8 months later, the same relapse occurred with spinal cord lesion load increase at MRI.

Therefore, despite the diagnosis of RRMS being mostly benign, in the case of our patient, given the partial and short-lasting response to several treatments and the risk of high-grade disability, we agreed on defining his MS form as aggressive RRMS.

Finally, once the negativity of the JCV titer was verified and the seroconversion with negative anti-natalizumab antibodies was confirmed, we decided to start natalizumab again, since it had been the only drug able to contain the disease for five years. However, at the end of 2021, we referred him to the department of hematology due to the sudden occurrence of fever resistant to broad-spectrum antibiotic therapy [11].

The CT/PET showed subcutaneous nodules in multiple body areas (not detectable with the naked eye), so a biopsy of the subcutaneous nodule of the right arm was performed, revealing a dense infiltrate localized to the subcutaneous fat in a pattern resembling lobular panniculitis. The infiltrate consisted predominantly of small-size lymphoid cells with irregular and hyperchromatic nuclei (CD3+, CD4−, CD8+, and ki67+), with a characteristic "rimming pattern" (proliferating lymphocytes around the adipocytes). They were proliferating and showed cytotoxic phenotypes.

SPTCL was finally diagnosed and first-line therapy with CHOP chemotherapy —Cyclophosphamide, Hydroxydaunorubicin, Oncovin (vincristine), and Prednisolone—was soon started, while natalizumab was interrupted. Unfortunately, one month later, new signs of disease progression occurred—subcutaneous nodules, diffuse ecchymosis, and generalized edema—and CHOP was shifted to the second-line therapy ESHAP (etoposide, solumedrol, high-dose cytarabine, and cisplatin).

One month later, he was tested positive to SARS-CoV-2, and during the infection period, he developed acute kidney disease, pancytopenia, increased triglycerides and ferritin, lower fibrinogen levels, splenomegaly, and dilatative cardiac disease. Therefore, a new diagnosis of concomitant SPTCL/hemophagocytic syndrome (HSP) was established (five out of eight diagnostic criteria); nevertheless, gemcitabine was introduced since ESHAP was not indicated in acute kidney disease.

Under gemcitabine treatment, the patient's vital signs improved with a marked reduction in kidney failure indices; therefore, after two cycles of gemcitabine, cisplatin was again introduced. Then, his performance status also recovered, and the other three cycles were needed to obtain a complete remission of symptoms.

To date, our patient is still disease-free and his neurological examination is stable. He was indeed restarted on natalizumab to control MS disease activity.

3. Methods

Reports of MS patients developing SPCLC and/or HSP were collected through a literature review using the Medline database. Keywords were ("natalizumab" AND/OR "alemtuzumab" AND/OR "ocrelizumab" AND/OR "rituximab" AND/OR "immunosuppressive therapy" AND "multiple sclerosis" AND "subcutaneous panniculitis-like T cell lymphoma (SPTCL)" AND/OR "hemophagocytic syndrome (HPS)").

4. Results

We identified five case reports and collected information regarding patients' age and gender, MS treatment during which they developed HSP, MS duration, the medications chosen to treat the hematological disease, and the follow-up (Table 1).

The patients' age range was 20–57 years; two were men and three were women. Three patients developed HSP after a cycle of alemtuzumab [12,13], one while under ocrelizumab [14], and another with interferon beta 1a [15].

No cases of SPTCL with MS were described, but there was one case of SPTCL in a patient treated with rituximab for chronic lymphocytic leukemia—not included in this table [16].

Corticosteroids were chosen for four patients, in one case combined with rituximab, in another with etoposide and cyclosporin. Just in one report was the interruption of interferon beta 1a resolutive.

Table 1. A review of the analyzed literature and our unreported case.

Author/ Year	Age	Sex	MS Duration	MS Therapies	Time between MS Therapy and SPTCL and/or HSP	Treatment for SPTCL/HSP	Follow-Up
Romero 2020 [12]	44	M	5	Glatiramer Acetate (2016) Alemtuzumab (2017/2018)	HSP 1 month after second cycle of Alemtuzumab	3-month tapering of methylpred-nisolone (0.15 mg/kg)	Good conditions 6 months later
Saarela 2018 [13]	20	F	N/A	Natalizumab (−/−) Alemtuzumab (−/−)	HSP 1 year after second cycle of Alemtuzumab	IV corticosteroids and a molecular adsorbent recirculation system procedure	Death after 1 month
Saarela 2018 [13]	28	M	N/A	Alemtuzumab	HSP thirty months after his first cycle of alemtuzumab	Responded to oral corticosteroid treatment for 4 months, combined with 2 doses of rituximab	Good conditions 6 months later
Machlańska 2020 [14]	32	F	9	Interferon beta 1 a (2012/2013) Ocrelizumab (2014–2018)	HSP 3 months after last cycle of Ocrelizumab	Etoposide, dexamethasone, and cyclosporine	Good conditions 1 year later
Cosso 2013 [15]	57	F	N/A	Interferon (IFN) beta-1a in the last 5 months	During the treatment with IFN	Spontaneous recovery after withdrawing IFN	N/A
Trinchillo (this work)	45	M	22	IFN beta 1A (2001–2011) Natalizumab (2011–2016) Alemtuzumab (2017–2018) Rituximab (2019) Ocrelizumab (2020) Natalizumab (2021)	During treatment with Natalizumab	CHOP 1 month ESHAP 1 month Gemcitabine + Cisplatin five cycles (the first two just gemcitabine)	Good conditions 1 year later

All patients recovered except one, who died one month after the onset of HSP. She was a young woman who developed HSP 1 year after the second cycle of alemtuzumab and was treated with IV corticosteroids.

5. Discussion

It is noticeable from our review that we report the first case of SPTCL with HSP in a multiple sclerosis (MS) patient.

With this case, we raise two crucial questions: (i) whether SPTCL might share common pathological features with MS or whether it might be triggered by one of the MS drugs; and (ii) which kind of treatment should be indicated when SPTCL with HSP occurs in the context of an autoimmune disease (AID).

A wide variety of lymphomas during AID has been described so far. Usually, SPTCL is associated with the hyperactivation of T-lymphocytes, and hence the concomitant diagnosis of SPTCL and T-cell-dependent AID (i.e., systemic lupus erythematosus or MS) is not surprising. Conversely, when SPTCL occurs in patients with B-cell mediated diseases or in patients undergoing immunosuppressive therapies, unveiling a common pathogenetic mechanism is more challenging and deserves to be further investigated [17].

In this regard, we might speculate that B-cell dysfunctional activation may produce a B-cell-dependent T-cell proliferation. For example, the concomitant occurrence of B-cell lymphomas and SPTCL was previously associated with the presence of TNF-alpha inhibitors or the inhibition of the cell-mediated and humoral immunity [18], which may cause a predominant and uncontrolled Th2 response, leading to rapid T-cell proliferation [19].

Similarly, the literature also presents some cases of panniculitis during treatments with rituximab. The association was explained with the peripheral B-cell depletion [16] and the reactive T clones' expansion, which fill the empty microenvironments created by the loss of B cells [20]. Moreover, natalizumab has also been associated with a few cases of B- and T-cell lymphomas; however, they were mainly central nervous system lymphomas and never associated with panniculitis [21–23].

In our case, the presence of a cellular mixed pattern at the biopsy [24] and the presence of multiple lesions [25] are typical presentations of lymphomas in immunocompromised patients; therefore, the immunosuppressive treatment seems to be the likeliest cause.

However, to discriminate which treatment was the one mainly responsible for such a disease is impossible, and the hypothesis of a trigger role for the sequencing of several immunosuppressants does not seem so unlikely.

MS is an unpredictable disease and treatment response is variable. To date, no drugs have shown to be completely efficacious, and neurologists need to switch therapies in the effort of controlling disease activity and eventually disability accrual. We call that approach "escalation" therapy and is currently debated, since an "induction" approach seems to be more effective. Moreover, the use of MS medications in sequence may indeed cause complications which otherwise would not occur [26].

For instance, when alemtuzumab follows other immunosuppressants, triggering another AID is even more frequent—as with our patient's AU; it may indeed cause immune events, mainly thyroid-related [27], even many years after the last cycle [28], while the use of ocrelizumab in the same conditions increases the risk of blood—but also breast, renal, and skin—cancers [29].

We can speculate that the occurrence of SPTCL—which is a T-cell-dependent blood cancer—correlates with the sequencing of the two mentioned antibodies.

Referring to HSP, cases associated with alemtuzumab, ocrelizumab, and rituximab have been described [12–14,30], and the hyper proliferation of a B-cell population in the absence of an effective T-cell regulation [31,32] has been proposed as the underlying mechanism. However, in secondary HSP, malignancies are the most common cause (60%); therefore, it is likely that, in our patient, HSP was due to SPTCL [33].

To answer the question about SPTCL/HSP treatment, at present, guidelines continue to evolve and there is no definitive consensus. For isolated SPTCL, current guidelines recommend high-dose systemic corticosteroids as the first line of treatment. In cases where SPTCL is severe or associated with HSP, CHOP chemotherapy is suggested. The ESHAP regimen is also considered as a second-line treatment option [8,31,34].

In contrast, the treatment of primary hemophagocytic syndrome typically involves corticosteroids or etoposide. If HSP is secondary, the underlying cause—whether infectious, inflammatory, or tumor-related—should be addressed during treatment [33].

Moreover, non-chemotherapy approaches have also been described in both hematologic conditions, like corticosteroids, cyclosporine, and autologous bone marrow transplants in SPTCL, and hematopoietic stem cell transplantation, emapalumab, alemtuzumab, anakinra, ruxolitinib, and tocilizumab in HSP. However, none of those has been officially accepted yet, since patients' response is very often influenced by genetic variants underlying both conditions, especially SPTCL [35–37].

Recent research has indeed begun to classify SPTCL based on genetic variants, particularly those affecting the HAVCR2 gene, and on epigenetic changes in the PI3K pathway. Such variants seem to influence the severity of the disease and the response to therapy. While these findings are promising, they come with risks due to their novelty and the

absence of a standardized protocol that mandates genetic testing for all patients with SPTCL [6,7].

Therefore, in our case, the hematologists preferred to follow the official guidelines to treat the patient. However, the patient's disease continued to worsen, and when he also developed an acute kidney disease, a well-known contraindication for several chemotherapy medications, they could just use gemcitabine, despite the fact that it is not the first choice in blood cancers and is less effective than the other drugs used for our patient.

Surprisingly, his disease was completely remitted, and we found some evidence in the literature which could explain that response.

First, an interesting study on the use of gemcitabine in MS should be cited.

That study suggests that gemcitabine may exert immunomodulatory effects reducing TH1 and TH17 cell proliferation and activation. That finding is particularly noteworthy, as these T cell subsets have been implicated in the pathogenesis of various autoimmune diseases, including MS. The ability of gemcitabine to prevent the onset of experimental autoimmune encephalomyelitis (EAE) in animal models provides further evidence for its potential role in mitigating autoimmunity and inflammation [38].

On the other hand, also in SPTCL, gemcitabine has shown some benefits, albeit in combination with other immunosuppressive drugs [39].

However, its role when both diseases are combined has never been explored so far, so we produced some hypotheses about the reason of this brilliant response.

Patients affected by concomitant SPTCL and AID may indeed have a worse phenotype, probably due to the autoimmune background, already damaged by the action of the T-cell basal population, and to the possible presence of germline or epigenetic mutation which also influence T-cell hyperactivation. Therefore, both the increase in number of those cells and their hyperactivity may have important effects, which are expressed with a more malignant phenotype.

On the other hand, T-cells are likely to develop in an aberrant way and with different markers because of several reasons: (i) the dysfunction of the tumor necrosis factor (TNF) and the major histocompatibility complex (MHC); (ii) the receptors' dysfunction; and (iii) the susceptibility of several genomic regions and loci to MHC [40,41].

For this reason, we believe that the T-cell tumor of our MS patient had an atypical treatment outcome to a first-line therapy because of the different genomic, proteomic, and MHC expression compared to non-MS patient T-cells.

6. Conclusions

We presented the first case of a patient with three concomitant resistant diseases (MS, HSP, and SPTCL) who surprisingly recovered with a first-line chemotherapy; after that, two other, stronger combinations were tried.

With this case, we strongly recommend always considering blood diseases as adverse events in MS patients treated with multiple drugs, especially immunosuppressants in sequence.

Moreover, we suggest also considering other kinds of therapies when such diseases develop in patients with autoimmune predisposition, because they are likely to respond to treatments which may be different from the ones suggested by the official guidelines.

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