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Review

Paraneoplastic Syndromes in Hodgkin's Lymphoma

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Abstract: Hodgkin's lymphoma (HL) is a monoclonal lymphoid neoplasm that is mainly characterized by multinucleated Reed–Sternberg cells on a background of non-neoplastic inflammatory cells. The incidence rate of Hodgkin's lymphoma is 2.5 new cases per 100,000 people per year (1). Paraneoplastic syndromes are conditions that are related to malignancy; however, they are not a result of tumor invasion or compression of malignant tissues. These paraneoplastic syndromes can occur virtually at any point in the disease course, and paraneoplastic syndromes in HL and their various forms are not well studied. In this review article, we will be discussing paraneoplastic syndromes in general and then delve into specific syndromes seen in HL, followed by a brief discourse regarding their early recognition and timely management.

Keywords: Hodgkin's lymphoma; paraneoplastic syndromes

Citation: Jadoon, Y.; Patil, G.; Loke, C.; Bhardwaj, P.V. Paraneoplastic Syndromes in Hodgkin's Lymphoma. *Lymphatics* **2024**, *2*, 25–42. https://doi.org/10.3390/lymphatics2010003

Academic Editor: Rahul Lakhotia

Received: 2 November 2023
Revised: 19 December 2023
Accepted: 26 January 2024
Published: 6 February 2024

1. Introduction

Hodgkin's lymphoma (HL) is a rare monoclonal lymphoid neoplasm with two main variants with distinct microscopic and clinical features: (1) classical and (2) nodular lymphocyte-predominant (NLP) HL. Classic HL has a characteristic microscopic finding of multinucleated Reed–Sternberg cells on a background of non-neoplastic inflammatory cells and accounts for approximately 95% of cases of HL. It is further characterized into subtypes including nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted. Conversely, nodular lymphocyte-predominant HL, representing approximately 5% of HL cases, does not have Reed–Sternberg cells; rather, it has characteristic lymphocyte-predominant (LP) cells surrounded by either B or T lymphocytes on histology. HL typically presents with painless lymphadenopathy, profound fatigue, and B symptoms, including fever, night sweats, and unintentional weight loss [1]. Compared to classic HL, NLP-HL tends to have a more indolent course, which often leads to earlier diagnoses and typically spares mediastinal lymph nodes. HL can also present without the classical aforementioned findings, as paraneoplastic syndromes (PNSs). PNSs are uncommon in HL, making their diagnosis particularly challenging. However, it is important to recognize these entities early as they can lead to earlier diagnoses of malignancy in cases where the PNS manifests before the malignancy itself, having the potential to impact clinical outcomes significantly [2,3]. In the years 2016–2020, HL had an incidence rate of approximately 2.5 new cases per 100,000, and the death rate was 0.3 per 100,000 people per year. Approximately 220,000 people in the US had HL in 2022. Over time, with therapeutic advances, the death rate of HL has been gradually declining without much change in the incidence of cases, leading to increasing prevalence [4]. Neurological syndromes are by far the most common type of PNS associated with HL, constituting nearly half of cases (42%) [5].

A systematic review of classic HL showed that the simultaneous diagnosis of PNSs and HL occurred in 42.2% of cases, and in 33.6% of cases, the diagnosis of HL antedated

the diagnosis of PNSs, while in 16.4% of cases, it was the diagnosis of PNSs that preceded that of HL [5]. Limited data also exist on the type of PNS in relation to the time of HL diagnosis. Paraneoplastic cerebellar degeneration is a type of PNS associated with HL, which tends to occur before the diagnosis of HL in approximately 80% of cases. Studies of limbic encephalitis (LE), another PNS associated with HL, showed that the delay between the onset of LE and HL ranged from 0 to 52 months, with a mean value of 8.5 months and a median of 6 months, amongst 11 cases [2]. It is difficult to determine how much these estimates are affected by the missed or delayed diagnosis of PNSs. Hence, our understanding of the temporality between HL and PNSs may change as we learn to better recognize PNSs associated with HL.

PNSs in HL are not well studied due to their low incidence, making their diagnosis and management challenging. This review aims to synthesize currently available data on PNSs related to HL to aid clinicians with their recognition and management.

2. General Overview of Paraneoplastic Syndromes and Pathophysiology

PNSs refer to a condition that is related to malignancy; however, it occurs neither by tumor invasion nor by compression of tissues by the tumor. They are also unrelated to infection, nutritional deficiencies, or treatment-related adverse effects. PNSs can occur at any point in the course of cancer and affect virtually any system. The diagnosis of PNSs requires the exclusion of alternative causes, which are usually more likely.

Although the pathophysiology underlying paraneoplastic syndromes is poorly understood, in general, there are two proposed mechanisms—nonimmune-mediated and immune-mediated (Figure 1).

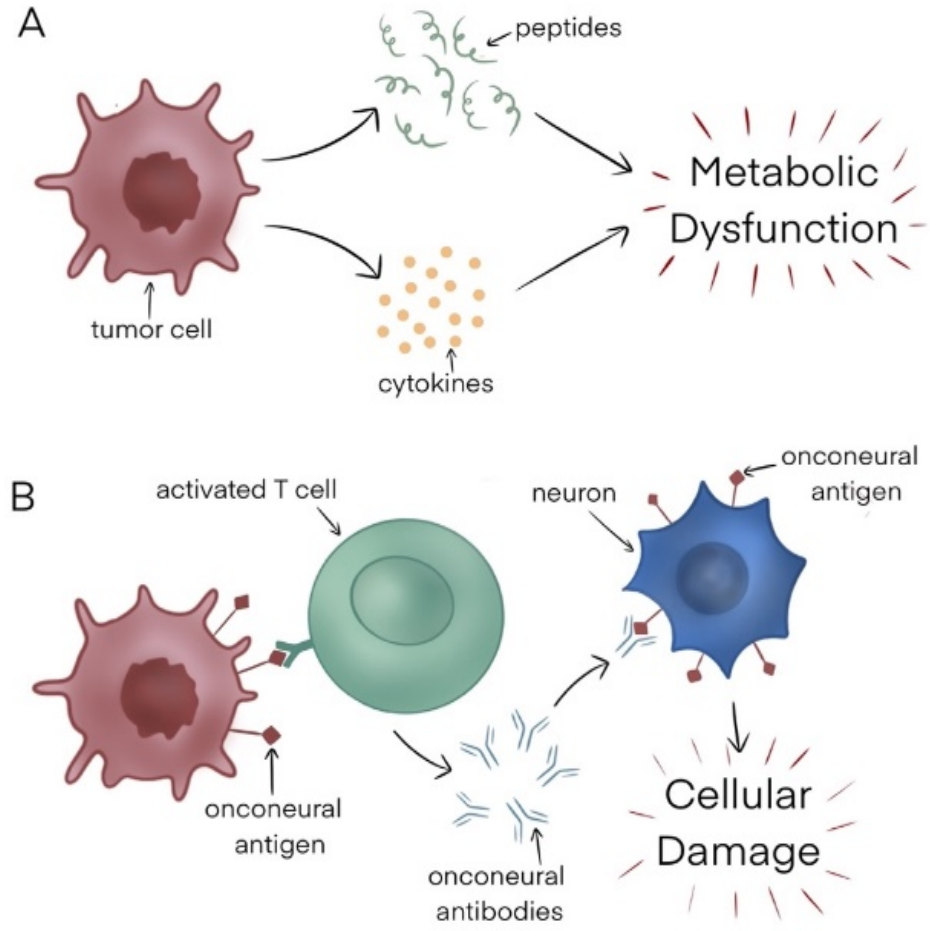

Figure 1. (**A**) Nonimmune mediated mechanism. (**B**) Immune-mediated mechanism.

Nonimmune mediated: One nonimmune mediated mechanism is the tumor secretion of various chemical entities, including hormones, cytokines, and peptides, which in turn impacts host tissues, leading to metabolic abnormalities that manifest as a constellation of symptoms. An example of this is hyponatremia caused by ectopic production of the antidiuretic hormone by small-cell lung cancer cells.

Another way PNSs may occur is when there is competition between the tumor and a specific system for a particular substrate. An example of this is tryptophan depletion caused by neuroendocrine tumors, resulting in carcinoid syndrome [6].

Finally, immunoglobulins produced by certain malignancies like Waldenstrom macroglobulinemia can react with the peripheral nervous system, resulting in several neurological manifestations.

Immune-mediated: Tumor cells may be highly immunogenic, with the ability to elicit both cell-mediated and humoral immune responses. This leads to immune cell activation by antigens present on tumor cells, stimulating the production of antibodies that can attack host tissues when their host and tumor antigens share biochemical similarities. For instance, myasthenia gravis is caused by acetylcholine receptor-directed antibodies, which are made in response to thymoma tumor cells.

3. Paraneoplastic Syndromes in Hodgkin Lymphoma by System

PNSs in HL can affect multiple organs, including neurologic, dermatologic, endocrine, hepatic, renal, hematologic, and rheumatologic. They appear to be more common in males and present across all stages of HL [5].

3.1. Neurological Syndromes

Paraneoplastic neurological syndromes are by far the most common subtype of PNS associated with HL, accounting for approximately 42.2% of cases [5]. The incidence of neurological PNSs in HL reported in population-based European studies ranges from 0.21 to 1.22 per 100,000 person years [7,8]. They often result from specific autoantibodies directed either against the underlying tumor cells, normal nervous system cells, or both. A paraneoplastic neurological syndrome care score (PNS-Care), proposed by a panel of international experts, can be used to aid in diagnosing these conditions [9]. It considers three components: clinical phenotype, detection of neuronal antibodies, and the presence of cancer. By scoring the patient in these areas, the diagnostic certainty of a condition being a paraneoplastic neurological syndrome is categorized as ‘definite’, ‘probable’, ‘possible’, or ‘non-PNS’, in decreasing order of certainty. The term ‘high-risk phenotype’ is now used when referring to syndromes that are classically characterized as paraneoplastic neurological syndromes. High-risk neurological phenotypes include rapidly progressive neurological syndrome, limbic encephalitis, encephalomyelitis, opsoclonus–myoclonus syndrome, sensory neuropathy, Lambert–Eaton myasthenic syndrome, and enteric neuropathy. The detection of onconeural antibodies can support a diagnosis of paraneoplastic neurological syndrome but on their own cannot definitively confirm nor reject a diagnosis of PNS. An onconeural antibody can be considered to be a ‘high-risk antibody’ (i.e., associated with cancer in >70% of cases), an ‘intermediate-risk antibody’ (associated with cancer in 30–70% of cases), or a ‘low-risk antibody’ (i.e., associated with cancer in less than 30% of cases). Table 1 shows onconeural antibodies associated with HL and describes the risk of association with malignancies as per the PNS-Care panel criteria [9]. Generally speaking, treatment options for suspected paraneoplastic neurological syndromes include IVIG (intravenous immunoglobulin), plasmapheresis, corticosteroids, cyclophosphamide, and rituximab when the concomitant lymphoma has not been identified [10]. It is important to note that paraneoplastic neurological syndromes, like PNSs in general, are diagnoses of exclusion.

Table 1. Onconeural antibodies associated with HL.

Antibodies	Risk of Association with Cancer	Associated Syndrome
Anti-Tr(DNER)	High risk	Cerebellar degeneration
Anti-Hu	High risk	Limbic encephalitis
Anti-NMDA	Intermediate risk	Limbic encephalitis
Anti-mGluR5	Intermediate risk	Limbic encephalitis
Anti-mGluR1	Low risk	Cerebellar degeneration

Anti-Hu: anti-Hu receptor. Anti-Tr(DNER): anti-delta/notch-like epidermal growth factor-related receptor. Anti-mGluR: anti-metabotropic glutamate receptor. Anti-NMDA: anti-N-methyl-D-asparate.

3.1.1. Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is amongst the most frequently cited PNSs associated with HL. The hallmark of PCD is severe loss of Purkinje cells of the cerebellum, causing subacute pancerebellar dysfunction. In 1976, Trotter et al. first detailed the discovery of antibodies targeting cerebellar Purkinje cells with the use of immunofluorescent staining in a patient with subacute cerebellar degeneration who was found to have HL. This suggested that Purkinje cells contain antigens that can cross-react with onconeural bodies produced as part of the host's immune response [11]. The term 'subacute cerebellar degeneration' is synonymous with 'rapidly progressive cerebellar syndrome'. Symptoms of this condition typically lead to severe disability within a period of 3 months [12].

The diagnosis of rapidly progressive cerebellar degeneration as a PNS requires the presence of truncal and limb ataxia [9]. Characteristic signs and symptoms of PCD include ataxia—both truncal and limb—dizziness, dysarthria, nystagmus, and diplopia, which are all cerebellar signs. This can be preceded by a prodromal syndrome with the occurrence of fever, nausea, vomiting, and headaches [13]. Marsili et al. describe anecdotal evidence of nuanced symptoms presenting months before the diagnosis of PCD including cognitive fluctuation during the same day, mild sensations of imbalance, dizziness, nausea, and vomiting [12]. Data supporting this diagnosis include classical imaging findings and the detection of high-risk antibodies. Magnetic resonance imaging (MRI) is the gold standard imaging modality to diagnose PCD, although it can be normal in the early course of disease. Hyperintensity of cerebellar hemispheres in T2 sequences appears to be the next chronological imaging feature, which is followed by the characteristic finding of cerebellar atrophy. Cerebrospinal fluid analysis may typically reveal pleocytosis or elevated protein levels in most patients, with a minority demonstrating oligoclonal bands [14]. While there are several different antibodies associated with PCD, the association is typically with antibodies to the Tr or delta/notch-like epidermal growth factor-related receptor (Tr/DNER) in HL [13–15]. These antibodies are usually detected in cerebrospinal fluid but can also be present in serum [16]. Another antibody that is associated with HL-related PCD is anti-mGluR1, which targets a glutamate receptor [17,18]. Autoantibodies against the intracellular Purkinje cell protein RGS8 have also been identified in one patient with HL and PCD, but further studies are needed to confirm this association [19]. The diagnosis of PCD typically precedes the diagnosis of HL by months to years, and treatment of the underlying lymphoma can lead to partial to complete remission of symptoms related to PCD, but this is infrequent [20–23]. There are reports of PCD presenting as a relapse of HL [16,18].

In general, the use of therapies beyond chemotherapy including corticosteroids, intravenous immunoglobulin (IVIG), cyclophosphamide, and tacrolimus does not seem to improve neurological outcomes in the majority of patients with PCD related to any malignancy [24]. With regard to HL specifically, management strategies have included either individual therapies or a combination of chemotherapy, steroids, IVIG, or plasma exchange, and even radiation chemotherapy alone with complete remission of neurological symptoms [18], partial remission [16], minimal improvement with severe disability, or no improvement [16,18,20,23].

While the dataset is very limited, outcomes appear to be better with improved response to treatment when PCD is diagnosed early. However, the treatment of HL takes precedence when concurrently diagnosed. In the urgent setting, IVIG +/− steroids and plasma exchange can be utilized. The Tr (or DNER) antibody titers usually disappear after HL treatment [21].

3.1.2. Limbic Encephalitis (LE)

LE is a neuropsychiatric disorder that classically presents with rapidly progressive symptoms including acute and subacute memory impairment, seizures, and psychiatric manifestations including anxiety, depression, and psychosis, which typically lead to severe disability within three months of symptom onset. There are numerous antibodies associated with LE and this condition can be paraneoplastic or nonparaneoplastic. Antibodies to mGluR5 are associated with HL-related PNSs [25]. The association of HL and memory impairment has been referred to as 'Ophelia syndrome' [26]. Characteristic MRI findings for LE include hyperintensity and swelling of mesial temporal lobes, which often exhibit an increase in a fludeoxyglucose-18 (FDG) positron emission tomography (PET) scan [27]. Supportive CSF findings include pleocytosis and oligoclonal bands [28]. In general, chemotherapy is an effective regimen, and ABVD (doxorubicin, vinblastine, bleomycin, and dacarbazine) is the most commonly used regimen and usually leads to partial neurological recovery at least and even complete recovery in some cases. Table 2 contains further details of cases of limbic encephalitis associated with HL.

Table 2. Neurological paraneoplastic syndromes.

Syndrome	Author(s)	Age and Sex of Patient(s)	Treatment Received	Clinical Outcome
Cerebellar degeneration	Arratibel et al. [20]	44-year-old male	IVIG initially but without clinical improvement, followed by ABVD with improvement	Complete resolution of HL with partial improvement in neurological symptoms
	Briani et al. [29]	16 patients (12 male and 4 female) with a mean age of 49 years (range 16–73)	Various treatments including combinations of chemotherapy for HL, IVIG, steroids, and plasmapheresis	8 patients had partial resolution of neurological syndrome after treatment of tumor. 2 patients died
	Bernal et al. [21]	28 patients (22 male and 6 female) with a median age of 16 (range 14–75)	Not mentioned	Complete remission of ataxia in three, partial in one; the rest of the patients stable, with bad functional status or worse
	Suri et al. [30]	54-year-old male	ABVD	Partial resolution of neurological syndrome
	Ypma et al. [31]	34-year-old male	EBVP	Complete resolution of HL and partial resolution of neurological syndrome
	Shams'ili et al. [32]	31-year-old	Antitumor treatment	Complete resolution of HL
		19-year-old	Antitumor treatment, steroid, and plasma exchange	Complete resolution of HL and functional deficits
	Spyridonidis et al. [33]	20-year-old male	Procarbazine, etoposide, doxorubicin, cyclophosphamide, bleomycin, prednisone, and field irradiation	Complete resolution of HL and no improvement in neurological syndrome

Table 2. *Cont.*

Syndrome	Author(s)	Age and Sex of Patient(s)	Treatment Received	Clinical Outcome
Cerebellar degeneration	Chepovetsky et al. [23]	68-year-old male	IVIG and CHOP	Partial resolution of HL and no improvement in neurological syndrome
	Smitt et al. [18]	19-year-old female	MOPP-ABV, followed by subtotal nodal irradiation, IVIG, and plasmapheresis	Complete resolution of HL and neurological syndrome
		49-year-old female	Plasmapheresis	Complete resolution of HL and no improvement in neurological syndrome
	Christensen et al. [16]	76-year-old male	IVIG, gemcitabine, liposomal doxorubicin, and radiotherapy	Complete resolution of HL and partial resolution of neurological syndrome
Limbic encephalitis	Briani et al. [29]	45-year-old male	Not mentioned	Complete resolution of neurological syndrome after treatment of tumor
	Lancaster et al. [34]	46-year-old female	ABVD and steroids	Partial resolution of HL and complete resolution of seizures and altered mentation
		15-year-old male	IVIG and radiotherapy	Complete resolution of HL and neurological syndrome
	Zandi et al. [35]	49-year-old male	Steroids, IVIG, plasmapheresis, and chemotherapy (regimen not mentioned)	Progression of HL and partial resolution of neurological syndrome
	Kung et al. [36]	53-year-old female	ABVD	Complete resolution of neurological syndrome
	Hentschke et al. [37]	61-year-old male	ABVD	Partial resolution of HL and partial resolution of neurological syndrome
	Bernard et al. [38]	59-year-old female	MOPP-ABV and radiotherapy	Complete resolution of HL and partial resolution of neurological syndrome
	Deodhare et al. [39]	23-year-old male	Steroids and ABVD	Complete resolution of HL and partial resolution of neurological syndrome
	Rosenbaum et al. [40]	13-year-old female	Chemotherapy (regimen not mentioned)	Partial resolution of HL and no improvement in neurological syndrome
		16-year-old female	Cisplatin, etoposide, and ifosfamide	Partial resolution of HL and partial resolution of neurological syndrome
	Duyckaerts et al. [41]	36-year-old male	Steroids, procarbazine, chlormethine chlorhydrate, and vincristine sulfate	Death
	Pfliegler et al. [42]	33-year-old male	MOPP followed by ABVD	Complete resolution of HL and complete resolution of neurological syndrome

Table 2. *Cont.*

Syndrome	Author(s)	Age and Sex of Patient(s)	Treatment Received	Clinical Outcome
PEMS	Briani et al. [29]	59-year-old female	Not mentioned	Partial resolution of neurological syndrome after treatment of tumor
		84-year-old male	Not mentioned	Not mentioned
PERM	Borellini et al. [43]	60-year-old male	Prednisone and ABVD	Complete resolution of HL and partial resolution of neurological syndrome
Pontine myelinolysis	Kanaparthi et al. [44]	11-year-old male	ABVD	Partial resolution of HL and partial resolution of neurological syndrome
GBS	Odaman Al et al. [45]	13-year-old female	ABVD, IVIG, and steroids	Partial resolution of HL and partial resolution of neurological syndrome
	Anderson et al. [46]	34-year-old male	IVIG and ABVD	Partial resolution of HL and partial resolution of neurological syndrome
CIDP	Briani et al. [29]	Males aged 48 and 62 years	Not mentioned	One patient had complete resolution of HL and partial resolution of neurological syndrome
Sensory neuropathy	Briani et al. [29]	61-year-old male	Not mentioned	Not mentioned
	Milanesio et al. [47]	36-year-old female	ABVD	Complete resolution of HL and partial resolution of neurological syndrome
Sensory neuronopathy	Briani et al. [29]	29-year-old female	Not mentioned	Not mentioned
Myotonia	Briani et al. [29]	70-year-old female	Not mentioned	Partial resolution of neurological syndrome after treatment of tumor
Lower motor neuropathy	Flangan et al. [48]	31-year-old female	IVIG, steroids, ABVD, radiation, ICE, and ASCT	Complete resolution of HL and partial resolution of neurological syndrome
GACNS	Johnson et al. [49]	49-year-old female	BCVPP and whole-brain radiation therapy	Complete resolution of HL and partial resolution of neurological syndrome
	Lopez-Chiriboga et al. [50]	25-year-old female	ABVD	Partial resolution of HL and partial resolution of neurological syndrome
	Delobel et al. [51]	26-year-old female	Prednisone, ABVD, and radiotherapy	Complete resolution of HL and complete resolution of neurological syndrome
Rhomboencephalomyelitis	Valappil et al. [52]	Female in her 50s	Not available	Not available

ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine. ASCT: autologous stem cell transplant. BCVPP: carmustine, cyclophosphamide, vinblastine, procarbazine, and prednisone. CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone. CIDP: chronic inflammatory demyelinating neuropathy. EBVP: etoposide, bleomycin, vinblastine, and prednisone. ICE: ifosfamide, carboplatin, and etoposide. GACNS: granulomatous angiitis of the nervous system. IVIG: intravenous immunoglobulin. MOPP: mechlorethamine, vincristine, procarbazine, and prednisone. MOPP-ABV: mechlorethamine, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, and vinblastine. PEMS: paraneoplastic encephalomyelitis. PERM: progressive encephalomyelitis with rigidity and myoclonus. PNS: paraneoplastic syndrome.

3.1.3. Granulomatous Angiitis of the Central Nervous System

This disorder is a necrotizing vasculitis that affects small vessels of both the venous and arterial systems of the leptomeninges, brain parenchyma, and spinal cord in the absence of systemic vasculitis. The pathophysiology behind this PNS in HL remains unclear. Most

patients present with neurological dysfunction prior to a diagnosis of HL with symptoms of headache, weakness, ataxia, confusion, or altered consciousness [50].

Diagnosis can be challenging depending on the vascular territory involved. A brain biopsy can help exclude other etiology including malignancies like intravascular lymphoma, secondary CNS involvement of HL, infection, etc., and thus confirm a diagnosis.

A combination of cyclophosphamide, steroids, and HL-specific chemotherapy has been seen to be an effective treatment [2,50].

Other less frequently encountered neurological PNSs have been described further in Table 2.

3.2. Hepatic Syndromes

3.2.1. Vanishing Bile Duct Syndrome (VBDS)

VBDS is a syndrome consisting of paraneoplastic intrahepatic cholestasis with the hallmark histological findings of intrahepatic bile duct loss. The exact mechanism behind this PNS remains unknown; however, it has been theorized to be either immune-mediated or related to cytokine production by tumor cells promoting cholestasis. This is a diagnosis of exclusion and a thorough work-up is necessary to exclude hepatic infiltration by tumor, lymphomatous liver infiltration, external biliary tract compression by tumor or lymph nodes, hemolysis, infections such as hepatitis and cytomegalovirus, autoimmune hepatitis, and the effects of hepatotoxic drugs, amongst others. A liver biopsy is necessary to make the diagnosis. Recognition of HL-related VBDS is of paramount importance, as the hepatic dysfunction can quickly progress to liver failure with high mortality if definitive treatment of HL is not promptly initiated; it can sometimes progress despite this, potentially requiring liver transplantation. A literature review by Ballonoff et al. suggested that this occurs mostly in males in their 30s and may occur across different stages of HL. Radiotherapy was often utilized to treat early-stage HL, as the use of traditional chemotherapies was limited by the degree of hepatic dysfunction. Early (stage I or II HL) disease at diagnosis, use of radiotherapy, and complete remission of HL were all associated with improved liver-failure-free survival at one year since diagnosis of VBDS [53]. Another review consisting of a total of 46 patients with VBDS conducted by Scalabrini et al. compared the usage of full vs. reduced dose upfront chemotherapy with resolution of VBDS. A total of 18 patients had resolution of VBDS and, of these, only one received a reduced dose regimen, suggesting the benefit of using standard dosing of chemotherapy initially. All of these patients with VBDS resolution also received upfront steroids and had a resolution of HL as well. The role of high-dose ursodeoxycholic acid in treating liver disease was also noted [54]. Various chemotherapy regimens have been utilized with varying degrees of success, as summarized in Table 3.

Table 3. Vanishing bile duct syndrome.

Author(s)	Patient Age in Years	Sex	Treatment Received	Clinical Outcome
Córdoba et al. [55]	17	Male	Modified regimen of bleomycin, cyclophosphamide, dacarbazine, and methylprednisolone	Complete remission of HL
Crosbie et al. [56]	21	Female	Modified regimen of mustine (10 mg), vincristine (1 mg), and procarbazine (50 mg, once monthly)	Complete resolution of HL
Yalçin et al. [57]	47	Female	Vincristine, bleomycin, cyclophosphamide, and prednisone for 2 cycles, followed by 8 weeks of radiotherapy	Symptomatic resolution of PNS and normalization of bilirubin levels

Table 3. *Cont.*

Author(s)	Patient Age in Years	Sex	Treatment Received	Clinical Outcome
Ripoll et al. [58]	28	Female	C-MOPP regimen followed by radiotherapy	Death
	23	Female	Once cycle of C-MOPP, followed by ABVD a few months later, followed by radiotherapy	Complete resolution of HL
Barta et al. [59]	41	Male	2 weeks of prednisone followed by radiotherapy	Complete resolution of HL
Leeuwenburgh et al. [60]	17	Male	MOPP regimen, followed by a reduced regimen of P(V)AG	Complete resolution of HL
Pass et al. [61]	12	Male	A modified MOPP-ABV regimen, followed by radiation therapy	Complete resolution of HL
	10	Male	Nitrogen mustard and prednisone, followed by the Stanford V regimen, which was given along with rituximab and IVIG for IgG deficiency	Partial resolution of HL followed by death due to aspiration secondary to status epilepticus
Wong et al. [62]	38	Male	Reduced ABVD, followed by cyclophosphamide, followed by autologous hematopoietic stem cell transplant with a conditioning regimen consisting of bischloroethylnitrosourea, etoposide, cytosine arabinoside, and melphalan	Complete resolution of HL
Anugwom et al. [63]	27	Female	Radiotherapy, high-dose dexamethasone, and a modified chemotherapy regimen consisting of rituximab, gemcitabine, and cisplatin, followed by ABVD	Complete resolution of HL

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine, C-MOPP: cyclophosphamide, vincristine, prednisone, and procarbazine, Modified-MOPP: nitrogen mustard and prednisone for 2 weeks, followed by 12 weeks of weekly chemotherapy (doxorubicin and vinblastine, both doses reduced by half initially, vincristine, which was dose reduced by 25%, and standard doses of bleomycin and etoposide), MOPP: mechlorethamine, vincristine, procarbazine, and prednisone, P(V)AG: prednisone, doxorubicin, and gemcitabine, Stanford V regimen: adriamycin and vinblastine, 25% dose reduction in vincristine, and full doses of bleomycin and VP-16.

In summary, the use of radiotherapy to treat underlying early-stage HL is a reasonable choice when faced with VBDS, as traditional regimens are hepatotoxic and generally not well tolerated. When chemotherapy is given upfront, dose adjustments for hepatic function are necessary, often with the elimination of doxorubicin, which may be resumed once hepatotoxicity has resolved.

3.2.2. Paraneoplastic Intrahepatic Cholestasis

This syndrome is very similar to VBDS, with the absence of ductopenia, which is theorized to be a precursor condition to VBDS. This is also a diagnosis of exclusion and a work-up similar to the one described for VBDS is crucial to arriving at this diagnosis. Dose-reduced chemotherapy can be used initially to minimize hepatotoxicity, with ursodeoxycholic acid and steroids as an adjunct. Standard chemotherapy regimens can be used once liver function tests have normalized [64].

3.3. Renal Syndromes

Nephrotic syndrome is one of the PNSs that is mainly demonstrated as intrinsic renal lesions associated with glomerular injury. Although the association between HL and renal PNS is difficult to prove, it may be supported by the temporal relationship

between the two manifested by improvement or resolution of symptoms with treatment of underlying malignancy.

The link between HL and nephrotic syndrome has been described before and is most often due to minimal change disease [65,66]; it is seen with classical HL in particular [67]. This association was first described in 1922 by Gagliano et al. and was the first recorded instance of paraneoplastic glomerulopathy [68]. The incidence of this entity is reported in the range of 0.6% to 1% of HL cases. The poor response of minimal change disease-type nephrotic syndrome to steroids and cyclosporine has been suggestive of underlying HL [69]. While minimal change disease is the most commonly seen glomerulonephropathy associated with HL, other forms have also been seen in association with HL. This includes focal segmental glomerulosclerosis (FSGS) [66], AA amyloidosis, crescentic glomerulonephritis [70], and immunoactoid glomerulopathy, which is characterized by Congo red-negative deposits in renal microtubules on biopsy [71].

The pathogenesis has been linked to the overexpression of certain paraneoplastics that result in both lymphomagenesis and renal manifestations [72]. In addition, renal manifestations are associated with the expression of VEGF and TGF-β1, which are reportedly increased in Reed–Sternberg cells in HL [73,74]. In the various case reports described, this entity was treated with chemotherapy using various regimens including OEPA (araneoplasticone, vincristine, doxorubicin, and etoposide) and ABVD [65]. There was resolution of renal manifestations in both scenarios.

3.4. Dermatological Syndromes

3.4.1. Eczematous Eruptions

Paraneoplastic skin conditions like diffuse hyperpigmentation, erythema nodosum, and acquired ichthyosis have been described in the literature [75–77]. The main pathophysiology is hypothesized to be T cell dysregulation and increased Th2 cytokine profiles conducive to atopy. There are reports of biopsy-proven chronic eczema diagnosed in a young woman preceding a diagnosis of HL [78]. The patient was later treated with ABVD chemotherapy. Her eczema resolved after the second cycle, suggestive of a paraneoplastic phenomenon.

3.4.2. Paraneoplastic Pemphigus (PNP)

PNP is characterized by diffuse mucocutaneous involvement resulting in painful blisters, skin erosions, and lichen planus-like eruptions. Non-Hodgkin's lymphoma and chronic lymphocytic lymphoma are classically associated with paraneoplastic pemphigus [79]. PNP has rarely been reported in association with HL, comprising approximately 0.6% of cases of PNP [77]. Steroids, along with typical standard HL therapy, have been seen to be effective treatment [80].

3.5. Other Hematological Syndromes

Autoimmune Cytopenias (AICs)

Various autoimmune cytopenias including autoimmune hemolytic anemia (AIHA), autoimmune neutropenia, and immune thrombocytopenia purpura (ITP) have been associated with HL, although the incidence is quite rare at <1% of patients [81]. They may occur prior to, concurrent with, or at the time of recurrence of HL or in complete remission after treatment. However, they most commonly appear to precede a diagnosis of HL [82]. Autoimmune hemolytic anemias in this context tend to involve warm autoantibodies and occur more often in men. Standard chemotherapy for AIC rather than steroids has been seen to be effective in all these cases. Adjuncts seen to be effective for AIHA include combinations of steroids, IVIG, and splenectomy [82]. Autoimmune neutropenia and thrombocytopenia have been seen to respond well to steroids [82,83].

3.6. Miscellaneous Paraneoplastic Arthritis

Paraneoplastic arthritis in general is hypothesized to be related to immune complex deposition in joints. Rarely, this can be associated with HL. A case report by Erlij et al. describes a patient presenting with symmetric, seronegative polyarthritis and acute renal failure about three months prior to a diagnosis of HL. Although his arthritis responded to steroids initially, he had a recurrence of renal failure which resolved only with ABVD chemotherapy [84]. Although polyarthritis did not recur like kidney dysfunction, its timing and lack of recurrence are certainly suggestive of paraneoplastic pathology related to HL. A combination of migratory polyarthritis and acute renal failure occurring prior to a diagnosis of HL was also demonstrated in a case report by Aruch et al. Knee joint arthrocentesis revealed an inflammatory, noninfectious arthritis which was refractory to steroid treatment. However, it resolved with ABVD chemotherapy [85]. Although paraneoplastic arthritis has been associated with antinuclear antibodies and rheumatoid factor in other malignancies [84], both these cases were seronegative.

Other miscellaneous PNSs associated with HL have been described in Table 4. Of note, twenty-three patients in this study had 'paraneoplastic cerebellar degeneration', one had 'subacute cerebellar syndrome', one had 'chronic mild, cerebellar ataxia', and one had Tr antibodies and symptoms suggestive of limbic encephalitis but normal MRI. The results were not split up among the aforementioned categories.

Table 4. Miscellaneous paraneoplastic syndromes.

Syndromes	Author(s)	Patient Age in Years	Sex	Treatment Received	Clinical Outcome
Mucocutaneous PNS	Jurkovic et al. [86]	39	Male	Not reported	Not reported
Alopecia areata	Kanaparthi et al. [44]	11	Male	ABVD	Partial resolution of HL
	Gong et al. [87]	46	Male	Topical and intralesional corticosteroids steroids, followed by ABVD	Complete resolution of HL and near-complete resolution of PNS
Paraneoplastic pruritis	Villafranca et al. [88]	20	Female	In chronological order: ABVD, GDP, hematopoietic stem cell transplant, gemcitabine–inorelbine, everolimus, CVP, GDP, bendamustine, GVD, cyclophosphamide–vinblastine–celecoxib, lenalidomide–cyclophosphamide, high-dose dexamethasone, brentuximab vedotin, oral etoposide, carboplatin–gemcitabine, thalidomide, and dexamethasone. Aprepitant and dexamethasone used specifically for PNS	Partial response of PNS, mostly with aprepitant, and partial response of HLwhich progressed and ultimately led to death by lymphoma-related airway compression

Table 4. *Cont.*

Syndromes	Author(s)	Patient Age in Years	Sex	Treatment Received	Clinical Outcome
Granulomatous dermatitis	Pei et al. [89]	47	Female	Chemotherapy. Regimen not reported	Not reported
	Tabata et al. [90]	73	Male	Etoposide, prednisone, doxorubicin, and cyclophosphamide. Clobetasol ointment and intralesional triamcinolone used specifically for PNS	Near-complete resolution of HL and partial resolution of PNS with plaque softening
Acquired ichthyosis	Riesco Martinez et al. [75]	80	Male	Dose-reduced COPP	Partial resolution of PNS
Paraneoplastic pemphigus	Marjon et al. [80]	76	Male	Prednisone, followed by GVD	Partial resolution of PNS
Nephrotic syndrome	Aruch et al. [85]	38	Male	Dexamethasone, followed by ABVD	Complete resolution of HL and PNS
	Spyridonidis et al. [33]	20	Male	Prednisone, followed by procarbazine, etoposide, doxorubicin, cyclophosphamide, bleomycin, and prednisone along with irradiation	Complete resolution of HL and PNS
	Sfrijan et al. [65]	9	Male	OEPA along with irradiation	Complete resolution of HL and PNS
	Farruggia et al. [91]	11	Male	Prednisone, followed by COPP/ABV and irradiation	Complete resolution of HL and PNS
		17	Female		
Paraneoplastic hepatitis	Deacon et al. [92]	28	Male	Prednisolone, followed by rituximab and cyclophosphamide, followed by prednisone, followed by dose-reduced R-CHOP	Complete resolution of HL and near-complete resolution of PNS with persistence of splenomegaly
Immune thrombocytopenia purpura	Poponea et al. [83]	74	Female	ABVD	Complete resolution of PNS and partial resolution of HL
Stiff person syndrome	Gutmann et al. [93]	55	Female	ABVD	Complete resolution of HL and partial response of PNS with resolution of muscular hyperactivity but persistence of muscle weakness

Table 4. *Cont.*

Syndromes	Author(s)	Patient Age in Years	Sex	Treatment Received	Clinical Outcome
PAVS	Villano et al. [94]	45	Male	Corticosteroids and IV cyclophosphamide, followed by ABVD	Complete resolution of HL and PNS—although digital ischemia had occurred by the time chemotherapy was started, resulting in amputation of 3/8 distal phalanges
	AlRasbi et al. [95]	65	Male	Dacarbazin, doxorubicin, and vinblastine, followed by bendamustine and dacarbazine	Near-complete resolution of HL and PNS with persistence of dry gangrene of one phalange

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine, COPP: cyclophosphamide, vincristine, procarbazine, and prednisone, CVP: cyclophosphamide–vincristine–prednisone, GDP: gemcitabine, dexamethasone, and cisplatin, IV: intravenous, GVD: gemcitabine–vinorelbine–liposomal doxorubicin, OEPA: methylprednisolone, vincristine, doxorubicin, and etoposidum, PAVS: paraneoplastic acral vascular syndrome, PNS: paraneoplastic syndrome, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

4. Challenges and Future Directions

With the increasing use of immune checkpoint inhibitors, we are seeing an increase in the incidence of paraneoplastic phenotypes of autoimmune neurological disorders, particularly amongst malignancies that are not typically associated with PNSs. Improved detection techniques undoubtedly also play a role in this. Theoretically, it does make sense that immunotherapy could amplify the immunological process leading to the development of PNSs, just as the antitumor effect is augmented, with uninhibited T cell activation [96]. Neurological adverse effects related to immunotherapy are particularly important as they are often complicated by long-term sequelae and can even be fatal [97]. A review by Farina et al. investigates the occurrence of neurological immune-related adverse effects (n-irAE) in 147 patients with malignancies receiving immune checkpoint inhibitor therapy. Out of this cohort, 20.4% of patients were determined to have paraneoplastic-like syndromes. Conditions that are deemed high risk to represent PNS, including rapidly progressive cerebellar syndrome, limbic encephalitis, Lambert–Eaton myasthenic syndrome (LEMS), and sensory neuropathy, were characterized as 'paraneoplastic-like syndromes'. Older age and the diagnosis of PNSs were both associated with poor neurological outcomes, including disability and death, in this study. The majority of patients were treated with immune-active therapies, which only consisted of steroids in 95.8% of cases. Other therapies included the use of intravenous immunoglobulin, plasmapheresis, immunosuppressants, and biotherapies [98]. Interestingly, immunotherapy can be used as a treatment modality for patients with paraneoplastic neurological syndromes who do not respond to first-line therapy, but data on this are limited [99].

Recognizing stereotypical clinical syndromes, testing for onconeural antibodies, obtaining imaging to look for specific findings associated with neurological paraneoplastic syndromes, and conducting a thorough work-up to exclude alternate diagnoses including direct tumor-mediated pathology are all important steps in arriving at the diagnosis of immunotherapy-triggered PNSs [97]. This is an emerging area of medicine and we will likely see more studies in the next few years, which will hopefully allow us to better understand and manage these conditions.

5. Discussion

A recent systematic review by El Fakih et al. with a composite of 128 patients best summarizes PNSs in classical HL. Neurological manifestations appear to be the most frequent PNS, and within this category, central nervous system (CNS)-related pathology was most common. This was followed by hepatic and then renal pathology, in order of decreasing frequency. Most cases did not have antibodies associated with them, which highlights the challenge these diagnoses present. In 54.7% of cases, the PNSs resolved with treatment of HL, and another 26.6% of patients showed improvement of the PNSs with residual symptoms remaining [5].

Paraneoplastic syndromes in Hodgkin lymphoma represent a rare manifestation, which can occur prior to or concurrently with the malignancy. Due to this rarity, there is a paucity of data pertaining to these conditions, which makes diagnosing as well as treating them a difficult task.

There is a paucity of data on the role of routine surveillance for cancer when PNSs are diagnosed in the absence of malignancy. Although some authors have advocated for routine surveillance every 4–6 months for 2 years following the diagnosis of a condition that is suspicious for a PNS [13], we recommend having a high degree of clinical suspicion and a low threshold to pursue imaging when they develop symptoms.

6. Conclusions

In conclusion, PNSs are conditions related to malignancy that are uncommon and, especially in HL, are a rare entity. It is imperative to gain knowledge of different clinical entities or presenting symptoms for established paraneoplastic syndromes. In patients with no history of HL, recognition of PNSs may help with early diagnosis and management of HL. In patients with HL, treatment with chemotherapy and syndrome-specific preferred therapy will significantly impact clinical outcomes.

Author Contributions: Y.J.—writing original draft and editing. G.P.—writing original draft, C.L.—review and editing, P.V.B.—conceptualization, writing (review and editing), supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: PB has received honoraria and stock options with Doximity.

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