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Review of Paraneoplastic Syndromes in Children with Malignancy

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A paraneoplastic syndrome (PNS) is a set of symptoms and signs that can accompany the formation of a cancer but is not due to its direct infiltration or metastasis. PNS results from the secretion of peptides or hormones by tumor cells or from an immunological cross-reaction between the tumor antigens and host antigens. In the adult population, PNS affects up to 15% of patients with cancer, but data on pediatric patients remain lacking. The remarkable fact is that PNS can precede an oncology diagnosis, even by months or years. PNS can involve virtually any organ of the human body. In children, the most commonly involved are the nervous system (encephalitis, opsoclonus-myoclonus syndrome), skin (pemphigus, alopecia areata, pruritic skin, pyoderma gangrenosum, skin nevi), rheumatologic (dermatomyositis, vasculitis), liver (atrophic biliary syndrome, idiopathic cholestasis), endocrine system (hypercalcemia, syndrome of inadequate secretion of antidiuretic hormone), kidney (nephrotic syndrome), or hematopoietic system (hemolytic anemia, thrombocytopenia, eosinophilia, thrombotic macroangiopathy, leukomoid reaction). PNS can accompany all childhood cancers, but is most common in Hodgkin lymphoma, acute lymphoblastic and myeloid leukemia, neuroblastoma, Wilms tumor, and sarcoma. Diagnosis of PNS should begin as early as the suspicion of its unusual course, lack of response to standard treatment, or prolonged duration. Diagnosis should include typical disease-specific tests and simultaneous imaging of the head and neck, abdomen, and pelvis, as well as a bone marrow biopsy to look for malignancy. PNS treatment mainly includes anti-tumor therapy and sometimes additional immunosuppressive therapy. This article aims to review PNS in children with malignancy.

Keywords: Paraneoplastic Syndromes • Child • Hematology • Oncogenes

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Introduction

Each year, approximately 400 000 children worldwide and 1200 in Poland receive a diagnosis of cancer, and there is a consistent increase in incidence [1,2]. The most common childhood cancers are hematological diseases, primarily leukemias [3]. Conditions that can accompany or even precede the development of cancer by many months and years are classified as paraneoplastic syndromes (PNS). PNS are defined as a group of symptoms occurring together with oncological disease, but not resulting from direct infiltration or the development of metastases, but rather from the release of hormones and peptides that affect host metabolic pathways or from immune system cross-reactions with neoplastic cells [4]. PNS is estimated to occur in up to 15% of oncological patients, being the second most common cause of mortality in this group (27%). Unfortunately, exact statistics for pediatric patients are not known [4]. Studies describing PNS in adults are common, but publications regarding pediatric patients are rare. Recognizing PNS is extremely important, as cancers in the pediatric group are curable in as much as 85.7% of patients [5]. PNS in children can involve all organs but most commonly involve the nervous system, skin, and hematopoietic system. PNS can accompany all cancers, but the largest number of described cases are Hodgkin lymphoma (HL), acute leukemia, and neuroblastoma. Oncological diagnosis of PNS should begin simultaneously with the diagnosis of the symptom itself, as part of so-called oncological vigilance. PNS treatment mainly includes treatment of the underlying disease and immunosuppressive therapy [6,7]. This article aims to review PNS in children with malignancy.

Review of PNS in Pediatric Oncology and Hematology

Cutaneous Syndromes

Cutaneous PNS are some of the most common in hematology and can affect up to 50% of patients. They are definitely more common in adults; however, they are also observed in children [8]. The diagnosis of cutaneous PNS involves the use of the Curth criteria, as shown in **Table 1**.

Table 1. Curth criteria for the diagnosis of paraneoplastic dermatoses [8].

The onset of dermatosis must be in close time interval to the onset of cancer
Both conditions must follow simultaneous paths
Dermatosis may not be part of any genetic syndrome
A specific dermatosis accompanies a specific cancer
The skin disease is rare in the general population
There is a high correlation of symptoms with cancer

Pruritus

Paraneoplastic skin pruritus has been defined by the Special Interest Group of International Forum of the Study of Itch as a systemic reaction associated with the presence of a solid tumor or neoplasm of the hematopoietic and lymphatic systems that is unrelated to the local presence of tumor cells or cancer treatment [9]. Although this phenomenon is relatively well understood among adult patients, data regarding the pediatric population is limited.

Previous studies among adult patients suggest that the prevalence of pruritus in hematologic malignancies is higher than in other cancers, at around 30% for non-Hodgkin lymphoma (NHL) and 15% to 50% for HL [10]. An analysis by Belzberg et al noted a strong association of pruritus with bone, skin, hepatic, and hematologic malignancies, among which acute myeloid leukemia, HL, NHL, and acute lymphoblastic leukemia (ALL) were predominant. In contrast, pruritus was not observed with tumors of the germ cells, biliary tract, eye, and nervous system [11].

The mechanisms responsible for the appearance of pruritus as PNS are poorly known. One study found a strong association of interleukin (IL)-31 and Th2 cytokine with pruritus in lymphoma and their high expression in malignant T cells [10].

Pruritus in the course of cancer may not be associated with any skin changes or may be characterized by secondary lesions, such as scratches or nodules. The sensation of itching alone can be a significant detriment to quality of life for patients, which can lead to insomnia and depression [10]. Therefore, it is essential to undertake prompt and effective treatment; however, to date, no clear therapeutic strategy has been developed.

Antihistamines H1, while often failing to relieve pruritus, when used overnight, can have a calming effect. Medications from the selective serotonin reuptake inhibitor group, such as paroxetine and fluvoxamine, have proven efficacy in the treatment of paraneoplastic pruritus. The effectiveness of tetracyclic antidepressants, opioid receptor antagonists, and aprepitant is also pointed out. Some authors also suggest the effectiveness of non-pharmacological methods, such as UVB light therapy. Cure of the underlying disease, namely cancer, is associated with resolution of the annoying pruritic symptom, and its reappearance can indicate a relapse [10].

Alopecia Areata

Alopecia areata (AA) is a non-scarring dermatological condition. AA involves regional hair loss. It is most often associated

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with autoimmune disorders (autoimmune thyroid disease, inflammatory bowel disease, diabetes mellitus, myasthenia gravis, rheumatologic arthritis), and can be related to chronic stress or a familial predisposition to AA [12]. Autoimmune processes, such as impaired cytokine expression, presence of antibodies to pigmented hair follicles, loss of immune tolerance to hair follicle antigens, and T-lymphocyte dysfunction, are thought to be behind the occurrence of AA as PNS [13]. As a PNS, the occurrence of AA is rare. Nevertheless, it is known to be found in the course of pediatric lymphoid proliferative diseases such as HL, most commonly affecting the hair of the head, eyebrows, axillae, and pubic region. In cases of HL, alopecia most often occurs as a result of PNS and is far less often the result of direct infiltration of the tumor into the skin [14]. In a study by Anderson et al, the incidence of AA among patients with HL was only <0.004% [15]. The time of occurrence of AA symptoms in the course of HL is known to vary. Some case reports indicate that alopecia can appear before the general symptoms of lymphoma as a harbinger of the disease, but sometimes it occurs simultaneously with HL symptoms. The literature describes that successful treatment of the underlying cancer leads to resolution of AA symptoms [16].

Pemphigus

Paraneoplastic pemphigus was not discovered until 1990 [17]. It is an autoimmune disorder that occurs in a small group of patients, with a prevalence in groups up to age 8 to 18 years and Hispanic ethnicity [18]. Among malignancies, it is most commonly associated with NHL, Castelman disease, chronic lymphocytic leukemia, sarcomas, and thymomas [18,19,20]. Thus, it is mainly associated with B-cell lymphoproliferation [18,19]. In up to two-thirds of cases, these lesions are diagnosed after the cancer has been diagnosed [21]. Although the disease has an extremely heterogeneous course, a common feature in all patients is severe stomatitis, the presence of anti-plakin antibodies (against envoplakin and periplakin) and against desmoglein 3, and a severe course unresponsive to standard treatment, often leading to death [17-19]. The most effective treatment for the lesion is removal of the tumor, with a generally unfavorable prognosis [18,19].

Café-au-Lait Spots

Although these lesions can also occur in up to 25% of healthy children, they should not exceed 6 in number and mostly 1 cm in diameter [22]. Multiple café-au-lait lesions can suggest the presence of genetic syndromes and, along with them, neoplasms [22,23]. This is especially true for von Recklinghausen syndrome, a type 1 neurofibromatosis associated with mutation of the *NF1* gene. In this disease, up to 96.5% of patients have multiple café-au-lait spots, constituting one of the primary symptoms suggesting the need for specialist consultation, especially in children under the age of 10 years [24]. Tumors that can accompany this syndrome are primarily pilocytic astrocytomas (15% of patients), gastrointestinal stromal tumors, pheochromocytomas, and juvenile myelomonocytic leukemia [23-25]. In addition, it can be accompanied by cancers such as acute lymphoblastic leukemia, Wilms tumor, and pleomorphic sarcoma [23]. Interestingly, the co-occurrence of café-au-lait spots, juvenile xanthogranuloma, and juvenile chronic myelogenous leukemia has also been confirmed. Children with the aforementioned skin manifestations have up to 20- to 32-times higher risk of developing leukemia than do healthy children [26].

Acanthosis Nigricans

Acanthosis nigricans (AN) involves the presence of thickened, hyperkeratotic skin with a dark-brown hue. It mostly accompanies benign metabolic diseases but can represent PNS. This is especially true in the hands and/or feet (25% include both locations), with the most common (66%) accompanying gastric cancer in older individuals [27]. In children, isolated cases of AN as a PNS have been reported, most commonly involving gastric adenocarcinoma (children aged 2-17 years), Wilms tumor (2-3 years), osteosarcoma (9-14 years), adrenocortical carcinoma, papillary thyroid carcinoma, and malignant deciduoma. Interestingly, the occurrence of AN preceded the oncological diagnosis in cases of Wilms tumor and osteosarcoma [28]. The diagnosis of paraneoplastic AN in children is important because, at this age, it most often accompanies benign diseases and can therefore be overlooked [27].

Pyoderma Gangrenosum

Pyoderma gangrenous (PG) is a neutrophilic dermatosis that is mainly a manifestation of systemic inflammatory diseases, primarily ulcerative colitis in children (74%) [29,30]. It is most common in adults; pediatric patients account for only 4% of those with PG [29]. PG can also represent a PNS, especially when it is unresponsive to standard steroid therapy [29,30]. In children, isolated cases have been reported linking the disease primarily to acute myeloid leukemia but also to acute lymphoblastic leukemia myelodysplastic syndrome [31-35].

Rheumatological Syndromes

Rheumatological PNS described among adult patients include vasculitis, dermatomyositis, polymyositis, and polyarthritis [36]. Furthermore, the relative risk of developing cancer in the population of those with dermatomyositis aged <45 years is 2.79, and 3.13 for those >45 years [8]. Although the incidence of rheumatologic disorders in pediatric patients with cancer is less common than that in adult patients, such cases also occur.

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This is confirmed by the case report of a pediatric patient by Shay et al, which presented a male patient whose rheumatologic symptoms were a harbinger of oncologic disease. Based on symptoms such as proximal muscle weakness, fatigue, and periorbital swelling, dermatomyositis was diagnosed and treated with prednisone. Subsequently, as a result of unilateral lymphadenopathy, the patient was referred for oncologic diagnosis, and HL was diagnosed [37]. Therefore, the authors suggest performing CT scans of the chest, abdomen, and pelvis in cases of newly diagnosed dermatomyositis, including in a pediatric patient, especially in the case of an atypical course of rheumatologic disease [8]. The pathogenesis of vasculitis progressing as a PNS is based on the toxic effects of cytokines produced by tumor cells, such as TNF-α. Joint damage, in turn, is caused by an inflammatory process taking place in the synovial membrane triggered by immune complexes present in the body and cross-reacting with antigens of tumor cells and normal body tissues, mainly antibodies against NXP-2 and TIF1-γ [8,37]. It is also supposed that chronic stimulation of the immune system in the course of autoimmune disease can predispose to the development of lymphoproliferative disease. It is noteworthy that standard corticosteroid therapy can mask the symptoms present in HL, thus delaying proper diagnosis [38].

Hepatic Syndromes

The development of liver dysfunction occurs in many malignancies and is common in lymphatic proliferative diseases. These disorders can be a direct result of infiltration of the organ by tumor cells, or they can occur in the form of PNS or as a result of cancer therapy through drug-induced liver damage or reactivation of hepatitis virus infection. Two of the more common hepatic PNS are vanishing bile duct syndrome (VBDS) and idiopathic cholestasis [39].

Vanishing Bile Duct Syndrome

VBDS can occur as a result of the development of a number of diseases with different etiologies, from infection, to adverse drug reactions, to malignancies that cause hormonal disturbances in the body. It is also observed in Allagil syndrome [40]. Theories regarding the development of VBDS include antibody-mediated damage to the biliary epithelium by direct action of T lymphocytes or by high levels of cytokines, which contributes to the induction of apoptosis [41]. VBDS is a progressive disease in which intrahepatic bile duct atrophy leads to the development of cholestasis, eventually resulting in terminal liver failure and death. The development of VBDS has been documented in the course of HL, in which it is considered as PNS [40]. Its main symptoms are pruritus, jaundice, and weight loss [42]. The co-occurrence of HL and VBDS results in a significantly worsened prognosis among patients [43]. In many cases, patients with potentially curable disease die from liver failure. VBDS was described in, among others, a study by Ballonof et al, in which 65% of the study group of 37 patients died from hepatic insufficiency [44,45]. Wang et al noted that noninvasive markers of VBDS in children can be γ-glutamyl transpeptidase level >446 U/L (sensitivity 87.5%, specificity 91.6%, AUC=0.948, $P<0.001$) and total cholesterol level >6.4 mmol/L (sensitivity 100%, specificity 89.8%, AUC=0.983, $P<0.001$) [46]. The treatment of VBDS is mainly based on the therapy of the underlying disease, thus chemotherapy, chemoradiotherapy, and immunosuppression [42]. For VBDS in HL, it is most important to undertake early aggressive treatment of the malignancy, with the use of brentuximab vedotin, for example, which can be an effective therapeutic option without profound liver damage [41]. In addition, the use of ursodeoxycholic acid as a hepatoprotective element is effective [43]. In some cases, when the progression of VBDS is advanced and results in hepatic failure, remission of the underlying disease alone is not sufficient, and a liver transplant is required. This is confirmed in the case of a 33-year-old patient described by Aleem et al, who, despite remission of HL, died of hepatic encephalopathy due to liver failure in the course of VBDS [47]. Numerous reports on the coexistence of VBDS and HL demonstrate the need to test for malignancy when VBDS is confirmed by biopsy [40,41].

Idiopathic Cholestasis

Idiopathic cholestasis can present as PNS developing with HL. It is a condition that resembles VBDS in terms of clinical symptoms; however, it does not result in biliary atrophy. Idiopathic cholestasis manifests as painless, progressive jaundice, and over time can lead to liver failure and death. The condition is rare but has been reported with pediatric HL. One patient was treated with corticosteroids; nevertheless, the patient died 8 months after the onset of cholestasis symptoms [38].

Endocrine Syndromes

Paraneoplastic endocrine syndromes usually appear after the oncological diagnosis. They occur as a result of ectopic release of hormones and peptides that functionally mimic physiological proteins. This leads to disruption of the hormonal regulation axis of the body and specific clinical symptoms. The main types of endocrine PNS described in pediatric oncohematology include hypercalcemia and syndrome of inadequate antidiuretic hormone secretion (SIADH) [48].

Hypercalcemia

Hypercalcemia is definitely more frequently observed in adult oncological patients (20-30%) than in pediatric patients (0.4-1.3%). The main childhood cancers it accompanies are ALL, rhabdomyosarcoma, hepatoblastoma, HL, NHL, chronic myeloid

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Table 2. Characteristics of paraneoplastic hypercalcemia [50].

Pathomechanism	Neoplasms	Frequency	Laboratory diagnostics
PTHrP secretion, the so-called humoral hypercalcemia	Solid tumors, NHL ($^2/_3$), T-cell lymphoma, CML	80%	↑PTHrP ↓/N PTH ↑/N 1,25-OH-D_3
Direct bone resorption through induction of RANK, IL-6, -3, -8, TNF pathways	Multiple myeloma, ALL, CML	20%	↓PTHrP ↓PTH ↓1,25-OH-D_3
Ectopic production of 1,25-OH-D_3	HL, NHL ($^1/_3$)	Rare	↓PTHrP ↓PTH ↑1,25-OH-D_3
Ectopic production of PTH	Rhabdomyosarcoma, solid tumors of the ovary, lung, thyroid	Rare	↓PTHrP ↑PTH ↑1,25-OH-D_3

ALL – acute lymphoblastic leukemia; CML – chronic myeloid leukemia; HL – Hodgkin lymphoma; NHL – non-Hodgkin lymphoma; PTHrP – parathyroid hormone-related protein; PTH – parathyroid hormone; 1,25-OH-D_3 – calcitriol; RANK – receptor activator of nuclear factor κB; TNF – tumor necrosis factor; IL – interleukin.

leukemia in accelerated or blastic phase, and neuroblastoma [49]. The presence of hypercalcemia is an unfavorable prognostic factor (except for leukemia), regardless of calcium levels [50]. An increased risk of developing paraneoplastic hypercalcemia has been observed in patients with ALL with older age (second decade of life), diagnosis of pre-B blast phenotype with abnormal expression of CD13, CD33 and t(17;19), initial leukocytosis <20×10^3/μL, and initial high calcium levels [51,52]. It is worth noting that in cases of rhabdomyosarcoma, hypercalcemia usually occurs later in the progression of the disease and is associated with resistance to treatment [53]. The pathomechanism of paraneoplastic hypercalcemia, with laboratory markers, is shown in **Table 2**.

The main symptoms of hypercalcemia are weakness, hypotonia, anorexia, weight loss or growth delay, polydipsia and polyuria, abdominal pain, vomiting, constipation, and bone pain, with consequent symptoms of renal failure, impaired consciousness, or pancreatitis [51]. The main therapies include induction of calciurea (0.9% saline solution [2-3 L/m^2] and furosemide), inhibition of osteoclastogenesis (pamindronate [0.5-2 mg/kg iv]), and inhibition of bone resorption (calcitonin (4-8 IU/kg sc/im). In addition, steroids (hydrocortisone [200-300 mg iv]), gallium nitrate (100-200 mg/m^2), and picamycin (25 μg/kg) are used [54].

Syndrome of Inadequate Antidiuretic Hormone Secretion

SIADH results from ectopic secretion of antidiuretic hormone (ADH) by tumor cells, causing hypoosmotic euvolemic hyponatremia. It mainly accompanies solid tumors of the central nervous system, namely neuroblastoma, astrocytoma, medulloblastoma, and prolactinoma, as well as Ewing sarcoma, teratoma, thymoma,

Table 3. Diagnostic criteria for syndrome of inadequate antidiuretic hormone secretion [48,56].

Parameter	Value
Serum sodium level	<130 or <135 mmol/L
Plasma osmolality	<280 mOsm/kg H_2O
Urina osmolality	>100 mOsm/kg H_2O
Sodium excretion in urine	>40 mmol/L
Exclusion of cortisol deficiency, renal failure, hypothyroidism, pseudohyponatremia, and dehydration	

HL, and NHL [48]. The incidence of SIADH during treatment of ALL with predominantly *Vinca* alkaloids (vincristine, vinblastine), as well as cyclophosphamide and platinum derivatives, especially in combination with azole antifungals, is also extremely relevant. SIADH affects 10.8% to 14.7% of children undergoing ALL chemotherapy (11.9% in Poland) [55]. The main symptoms of SIADH are nausea, vomiting, headache, fatigue, gait disturbances, muscle cramps, anorexia, confusion, and, as the phenomenon becomes more severe, seizures, respiratory depression, and coma [48,55,56]. The diagnostic criteria for SIADH are outlined in **Table 3**. Treatment is based mainly on therapy of the underlying disease, and in cases of a severe, acute course, 100 mL of hypertonic (3%) salt solution can be used, correcting sodium levels by up to 4 to 6 mmol/L within 6 h [56].

Nephrotic Syndrome

Nephrotic syndrome is primarily caused by uncompensated urinary protein loss, as well as hypoalbuminemia, edema, lipemia,

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and hypercoagulability. The literature contains limited evidence linking nephrotic syndrome and hematologic malignancies of childhood, such as leukemia, HL, and NHL.

Nephrotic syndrome has been best described in pediatric patients with HL. It most often manifests as minimal change nephropathy (rarer as glomerulonephritis, focal segmental glomerular sclerosis or membranous glomerulonephritis). The nephrotic syndrome appears up to several months after the diagnosis of malignancy, and its incidence in this group of patients is only up to 1%. Stephan et al found that 5 of 483 children with HL, over a period of 13 years, developed proteinuria [57]. Proteinuria can be the only symptom of paraneoplastic nephrotic syndrome, providing a valuable clue to the diagnostic process. Also, failure of treatment of renal symptoms with glucocorticosteroids can suggest the coexistence of lymphoma. The exact pathomechanism of the appearance of nephrotic syndrome in this condition is not well understood, but it is presumed to arise in the process of T-lymphocyte dysfunction and, consequently, the accumulation of immune complexes. This leads to increased permeability of the glomerular basement membrane. With early diagnosis of HL, secondary nephrotic syndrome requires only conservative treatment, while renal function remains unchanged [58]. Farruggia et al published the description of 2 cases in which HL and nephrotic syndrome coexisted, and after administration of chemotherapy and radiotherapy, the patients had maintained remission of both diseases for 4 years [59]. Nevertheless, constant observation is necessary, as the onset of PNS can emerge up to 5 years after treatment of a hematooncological disease. It is necessary to monitor renal function during and after treatment, because recurrence of nephrotic syndrome can signal a relapse of the lymphoma [38].

Hematological Syndromes

PNS could also affect the hematopoietic system. Hematological syndromes manifest mainly as autoimmune cytopenias, affecting all cell lines. They can appear before, simultaneously with the diagnosis, or after treatment of the underlying disease, or even during relapse of the proliferative process. It is often difficult to distinguish whether the disorder is paraneoplastic or merely comorbid with the neoplasm; the latter is suggested by the occurrence of cytopenias before diagnosis and during treatment. The most common hematologic syndromes are autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) [38].

Autoimmune Hemolytic Anemia

AIHA is secondary in up to 60% cases and can accompany malignancies such as NHL or chronic myeloid leukemia, less commonly HL, and by far, least commonly the solid tumors ovarian or renal cell carcinoma [60,61]. Moreover, it is thought that the occurrence of AIHA is a harbinger of future lymphoproliferative disease in up to 20% of cases. An association between AIHA and HL has been found in clinical stage III and IV nodular sclerosis or the mixed form of HL [61]. Two conditions are required for the diagnosis of AIHA: the presence of hemolysis with anemia and a positive direct Coombs antiglobulin test [62]. Among the main pathomechanisms of the development of this syndrome are the production of autoantibodies by tumor cells, or increased activation of B lymphocytes, and the production of antibodies (mainly IgG, although also IgM and IgA) directed against tumor cells and cross-reacting with erythrocytes [58]. The main treatment for paraneoplastic AIHA involves steroids (prednisone, 2 mg/kg/day). Second-line treatment includes rituximab (375 mg/m^2/week), cyclosporine (5-6 mg/kg/day), intravenous immunoglobulin infusions (IVIG, 1 g/kg), and red blood cell concentrate transfusions [63].

Immune Thrombocytopenia

ITP is an autoimmune disease whose mechanism involves the accelerated destruction of platelets in the reticuloendothelial system. The syndrome can accompany HL and much less frequently, NHL. In patients with HL, the incidence of the syndrome is estimated at 0.2% to 1%. The mechanism of onset is suspected to be an excessive immune response to tumor cell proliferation, resulting in platelet destruction by antibodies of the IgG class or involving a component and IgM antibodies. Making the diagnosis can be delayed by the inability to collect material for histopathological examination because of the too low thrombocytes count. If there has been a rapid cessation of ITP symptoms, an association between ITP and HL may be suggested [64,65]. In a study by Schifferli et al, conducted from 2004 to 2019, a total of 3974 children were initially diagnosed with primary ITP. The diagnosis of 113 children in this group was eventually changed to secondary ITP and, in 7 of them, ITP appeared secondary to a malignancy (3 cases of myelodysplastic syndrome, 1 case of HL, 2 cases of myeloproliferative disease, and 1 case not matched to any specific malignancy due to lack of follow-up). Only 1 patient had received platelet-enhancing treatment in the form of corticosteroids or IVIG. After 12 to 24 months, 1 patient still had features of thrombocytopenia in laboratory tests [66]. ITP can also develop secondary to neuroblastoma. In that case, the thrombocytopenia at the time of diagnosis is usually associated with tumor infiltration of the bone marrow. Rapid disappearance of the symptom after surgical removal of the tumor can indicate its secondary nature. However, most patients require treatment in the form of IVIG, corticosteroids, and platelet concentrate transfusions [67].

Paraneoplastic Eosinophilia

Eosinophilia is an elevated level of eosinophils in the peripheral blood of >0.5 G/L. Based on severity, it can be described as

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mild (0.5-1 G/L), moderate (1-1.5 G/L), and severe (>1.5 G/L). Among the most common causes of this condition are parasitic diseases (80%). Eosinophilia may represent one of the PNS, which occurs in 0.8% of patients with this condition [68]. In adults, it occurs primarily with prostate, colon, breast, ovarian cancers, and HL [69]. In children, it occurs most often at ages <1 year and 3 to 5 years, accompanying such neoplasms as ALL, acute myeloid leukemia, teratoma, neuroblastoma, and fibroblastoma [68]. Interestingly, Cetinkaya et al reported that paraneoplastic eosinophilia is most often benign, while Burris et al indicated that it is severe (>5 G/L) [68,70]. Xu et al noted that eosinophilia in ALL is caused by the chromosomal aberration *ETV6: : ACSL6* and overexpression of the gene for IL-13 and enhanced inflammatory response. Interestingly, they also noted that in patients with hypereosinophilia, the addition of bromodomain inhibitor (JQ1) to the standard chemotherapy used to treat ALL can contribute to better therapeutic outcomes and a lower risk of relapse [71]. This may be a good alternative to the typical steroid treatment for eosinophilia in ALL. Hypereosinophilia in ALL is also associated with the t(5;14)(q31.1;q32.3) translocation, also causing overproduction of IL-3 and, through its action, stimulation of eosinophil production [72]. The differential diagnosis of eosinophilia, despite the significant prevalence of parasitosis as its cause, should always include malignancy, especially when clinical and laboratory symptoms do not resolve after the first phase of antimicrobial treatment.

Thrombotic Microangiopathy

Most often, thrombotic microangiopathy in pediatric malignancies occurs as a complication of treatment, as graft versus host disease after HSCT or as concomitant infection after cancer diagnosis [73-75]. The occurrence of thrombotic microangiopathy manifested in the form of hemolytic uremic syndrome (HUS) before cancer diagnosis concerns only a few described cases. All of them were associated with ALL in children aged 3.5 to 11 years [75-81]. Two cases (Salcedo et al, Piel et al) showed a prodrome of diarrhea, 8 months and 7 weeks away from the hematologic diagnosis, respectively [79,81]. In 1 case (Sinha et al), the diagnosis of HUS and ALL was made simultaneously [76]. For the remaining cases, the interval between diagnoses ranged from 1 to 5 months [77,78,80]. The likely pathogenetic factors responsible for the coincidence of the 2 diseases are TNF- α, IL-1β, IL-6, and IL-8, which are found in elevated levels in patients [76]. Induced inflammation contributes to vascular endothelial damage and HUS symptoms. Of note, in all cases are negative blood cultures, hepatosplenomegaly and, in some, cervical lymphadenopathy, symptoms not typically seen in HUS [76-81]. Their appearance is therefore an appropriate indication to suspect a paraneoplastic nature of the disease.

Paraneoplastic Granulocytosis

Paraneoplastic leukomoid reaction in children is extremely rare. It involves a white blood cell count of more than 50 000 G/L, marked mature neutrophilia, and a left shift and is not the result of an inflammatory process, infection, or hematologic malignancy per se [82]. In children, it is most often associated with cancers, especially nasopharyngeal, HL, melanomas, and sarcomas, but it remains a casuistic condition [83-85]. It is caused by tumor cells secreting factors such as hematopoietic growth factors granulocyte (G-CSF), granulocyte monocyte (GM-CSF), and IL-6, which stimulate overproduction of white blood cells [83]. The basis of diagnosis is to adequately distinguish this type of reaction from the leukemic process, including by performing a bone marrow biopsy with immunophenotyping and thorough imaging studies [83-86].

Neurological Syndromes

PNS can affect different areas of the central and peripheral nervous system and neuromuscular connections and muscles, occurring separately or in combinations. The symptoms are usually severe and can lead to disability or even death [87]. Although the literature describes the presence of antibodies against antigens expressed in both the tumor and the nervous system (onconeural antibodies), their presence can be demonstrated in less than half of patients with PNS. In view of this, the absence of antibodies cannot be the basis for ruling out PNS in a symptomatic patient [87,88]. However, the literature abounds with reports that patients who develop neurologic PNS have a better prognosis than patients with histologically identical tumors but without neurologic PNS [87].

The diagnosis of PNS in children is based on the general criteria used in adults; however, the maximum period between the onset of neurological symptoms and the appearance of a tumor, which is 5 years in adults, should be shorter in children. This is due to the different epidemiology of tumors in children (higher incidence of neuroblastoma, teratoma, HL), and the occurrence of nervous system symptoms that can mask the symptoms of the cancer and delay its diagnosis [87].

Paraneoplastic symptoms in children most often involve the central nervous system, and the most common syndromes include opsoclonus-myoclonus syndrome (OMS), limbic encephalitis, and encephalitis with antibodies against the N-methyl-D-aspartate receptor (anti-NMDA-R) [87,89].

Opsoclonus-Myoclonus Syndrome

OMS is the most common neurological PNS in children. It is also sometimes called Kinsbourne syndrome or “dancing eyes”

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syndrome [87]. Typical for this syndrome is the presence of abnormal eye movements (rapid, involuntary eye movements in all directions, of high frequency and large amplitude, with no intersaccadic interval), myoclonus, ataxia, and behavioral changes [90,91]. OMS can initially include episodes of bewilderment and falls, with sequential addition of symptoms such as myoclonus, salivation, speech disorders, hypotonia, and sleep disturbances. It usually takes between 1 week and 20 months from the onset of neurological symptoms to the diagnosis of malignancy. The syndrome is most commonly associated with latent neuroblastoma of low-grade malignancy (stage I or II) and mainly affects children aged 6 months to 3 years [87,91]. As many as 50% of patients with OMS receive a diagnosis of neuroblastoma, although only 2% to 3% of children with neuroblastoma receive a diagnosis of OMS [89]. The onset of symptoms is mostly related to the presence of antibodies. Interestingly, OMS results from an increased immune response mediated by T and B lymphocytes [87]. In the diagnosis of this syndrome, it is recommended to simultaneously look for the presence of anti-neural antibodies and the primary tumor. The presence of antibodies alone does not confirm the paraneoplastic nature of the lesion [85]. In particular, magnetic resonance imaging (MRI) or positron emission tomography scanning is recommended to look for neuroblastoma and tumors in the abdomen, pelvis, and testes in boys [87,90]. Treatment usually includes systemic immunosuppression with corticoids (especially in 52-week protocol), plasmapheresis, and IVIG, and therapy of the underlying disease with chemotherapy (with good response to rituximab) [87,92]. Unfortunately, the onset of OMS is often associated with permanent neurological consequences; however, intensified treatment can alleviate the negative effects of this syndrome [90,91].

Limbic Encephalitis

Typical features of this syndrome include personality changes, irritability, seizures, cognitive impairment, and memory loss. We can expect to see these symptoms primarily in children affected by HL, ovarian teratoma, or testicular tumor. In adults, limbic encephalitis precedes cancer diagnosis in 60%, a median of 3.5 months. Although exact data are lacking, this percentage is estimated to be higher in children [87,91]. Diagnosis among adults is clinical and based on cerebrospinal fluid analysis, MRI, or electroencephalogram. The sensitivity and specificity of the aforementioned methods have not been thoroughly investigated among children. The presence of antibodies is found in 60% of patients. The most common are antibodies to the VGKC complex. In children with the presence of these antibodies, the first symptoms may be epileptic seizures, which can be accompanied by signs of encephalopathy [93]. Treatment of limbic encephalitis includes treatment of the underlying disease and the use of immunomodulatory therapies. Depending on the case, antiepileptic drugs and psychopharmacological agents are used supportively. The prognosis is poor, especially in patients with the presence of antibodies [88].

Anti-NMDA Receptor Encephalitis

Although the syndrome was first described in 2007, hundreds of cases have been reported in the literature over the years. Adolescent patients have symptoms such as behavioral or personality changes, sleep disturbances, dyskinesia or dystonia, autonomic system disorders, and speech disorders [87,89]. A pattern of symptoms can occur in young women. About 70% of them have prodromal symptoms, such as headache, nausea, diarrhea, fatigue, fever, or signs of upper respiratory tract infection. Over the next several days, psychiatric symptoms appear, such as mania, paranoia, and anxiety disorders. Wrong diagnosis of newly identified psychiatric illness is often made at this stage. Then, within a month after the first symptoms, they are accompanied by dyskinesia, seizures, disorders from the autonomic nervous system, and disturbances of consciousness, which can even lead to the need for mechanical respiratory support [92]. Additional tests show lymphocytic pleocytosis or oligoclonal bands and increased protein level in the PMR, as well as abnormalities in electroencephalogram and MRI [88]. Anti-NMDA encephalitis is primarily associated with teratoma [89,94].

Other Neurological Syndromes

The patient with HL has been described to have cerebellar degeneration and Horner syndrome, while neuroblastoma can occur with Lambert-Eaton myasthenic syndrome [6,89]. Another tumor-associated encephalitis can be anti-Ma2 encephalitis, almost always associated with the presence of a testicular tumor or germ cells and anti-neural anti-Ma2 antibodies [48]. Its symptoms include a combination of encephalopathy, damage to the cortex and thalamus, and abnormal eye movements [48]. Extremely rarely, children with thymoma can develop myasthenia gravis, characteristic of adults [6]. Dermatomyositis can also occur, as cases have been reported in children with immunoblastic sarcoma and germ cell tumor of the ovary [6,7].

Ophthalmological Syndromes

In addition to the aforementioned OMS syndrome, with rapid, involuntary eye movements in all directions of high frequency and large amplitude, anti-Ma2 inflammation, with which eye movement abnormalities such as nystagmus and vertical paresis are characteristic, and anti-NMDA inflammation, which can be accompanied by visual disturbances and visual acuity, ophthalmologic disorders can constitute PNS [6,7]. Among these are cases of ophthalmoplegia accompanying glioblastoma multiforme [95]. Ocular symptoms in OMS are associated with the presence of antinuclear antibodies type 1 and 2 and

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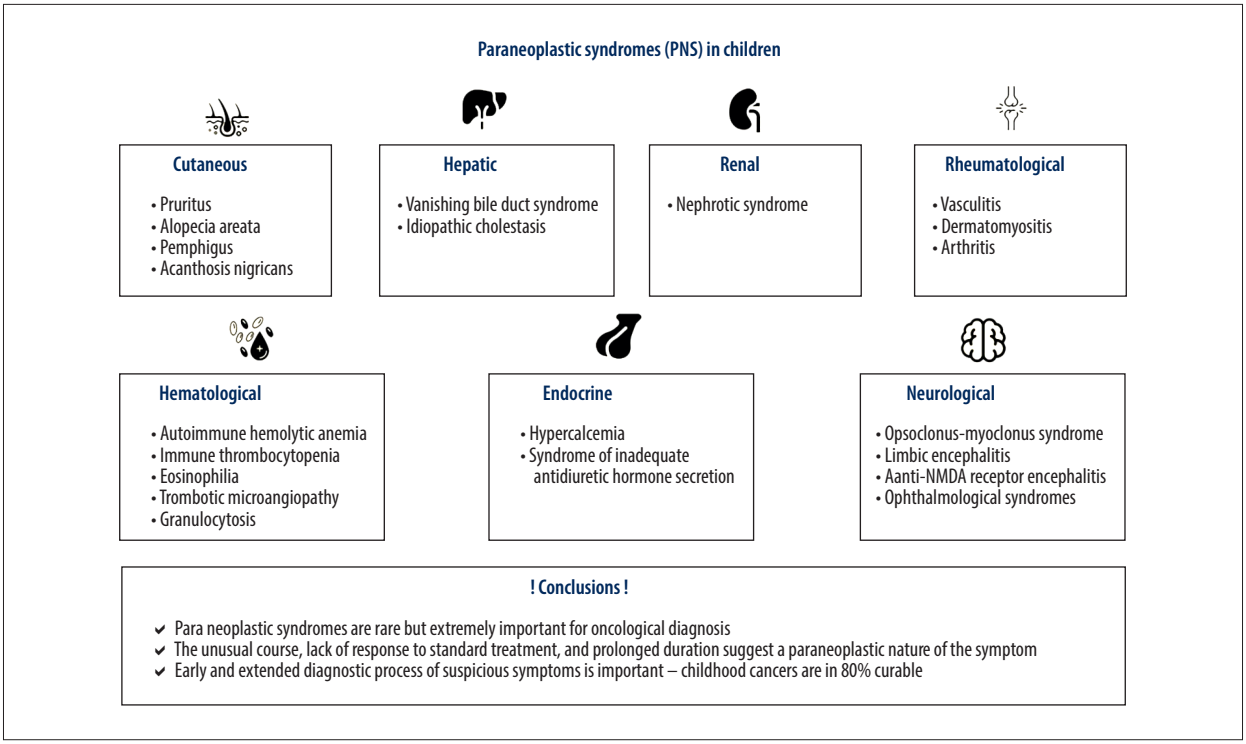

Figure 1. Review of paraneoplastic syndromes in pediatric oncology and hematology.

damage to Purkinje cells in the cerebellum and pontine neurons [96]. Ocular symptoms (ptosis, diplopia, abnormal eye movements) also accompany myasthenia gravis, which is rare in children, and Lambert-Eaton syndrome [96].

The PNS shown above are summarized in **Figure 1**.

Future Directions

PNS in pediatric patients are extremely rare. Epidemiological studies on larger groups of patients are definitely lacking on this topic. Further case reports and reviews are also needed to identify risk factors and effective therapeutic approaches in pediatric patients with PNS. It would also be useful to have guidelines that address precisely the diagnostic algorithms for each syndrome, as well as the features that would prompt the moment when oncologic diagnosis should be initiated.

Conclusions

PNS are not common phenomena but have remarkable diagnostic value. They can affect almost any system of the body. They often precede overt symptoms and cancer diagnosis by up to several months or years. Therefore, any symptom or, even more so, a set of symptoms that do not respond to the typical treatment or occur in high-risk patients should alert the physician to the need for extended early diagnosis in search of cancer. This is extremely important among pediatric patients because of the incredibly high cure rate of more than 80% for all types of cancer and the higher success of therapy if the disease is detected quickly.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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