

Paraneoplastic syndromes in patients with melanoma

Michał Dec, Hubert Arasiewicz

Department of Dermatology and Vascular Anomalies, John Paul II Centre of Paediatrics, Sosnowiec, Poland

Adv Dermatol Allergol

DOI: <https://doi.org/10.5114/ada.2024.141114>

Abstract

Paraneoplastic syndromes are a group of rare clinical conditions characterized by a diverse array of systemic manifestations that arise in association with malignant tumours, often due to the production of bioactive substances by the tumour or an autoimmune response to the tumour. Melanoma, a malignant skin neoplasm originating from melanocytes, has been associated with various paraneoplastic syndromes. This paper provides an overview of the key paraneoplastic syndromes observed in patients with melanoma. Paraneoplastic syndromes in melanoma can manifest with neurological, dermatological, endocrine, haematological, and rheumatological symptoms, among others. Melanoma-associated retinopathy was the most reported paraneoplastic syndrome; this entity is characterized by a spectrum of retinal abnormalities. Paraneoplastic neurological syndromes, such as paraneoplastic encephalitis and paraneoplastic cerebellar degeneration, are among the most frequently reported. The pathophysiology of paraneoplastic syndromes often involves the production of autoantibodies against neuronal or tumour antigens, immune-mediated reactions, or the release of cytokines and growth factors from the tumour. Management strategies for paraneoplastic syndromes associated with melanoma primarily focus on treating the underlying malignancy, which may lead to resolution or improvement of the paraneoplastic manifestations. Immune-modulating therapies, including corticosteroids, intravenous immunoglobulins, and plasmapheresis, may be considered in selected cases to ameliorate symptoms and suppress the autoimmune response. In conclusion, paraneoplastic syndromes in patients with melanoma are a complex and diverse group of clinical entities with a broad range of presentations. Further research is needed to enhance our understanding of the mechanisms and therapeutic options for paraneoplastic syndromes associated with melanoma.

Key words: melanoma, paraneoplastic syndrome.

Introduction

Paraneoplastic syndromes (PNS) refer to nonmetastatic tumour-associated manifestations that arise from malignancies located in distant anatomical sites. In certain instances, PNS may present as the initial or predominant clinical indication of an underlying cancer. Consequently, the prompt recognition of PNS can aid in the investigation of an as-yet undiagnosed malignancy. While the skin is commonly affected by peripheral nervous system (PNS) disorders, occurrences of PNS in skin neoplasms, including aggressive ones like malignant melanoma, have been infrequently documented. Herein, we compile the reported evidence of PNS associated with the growth of malignant melanoma. The objective of our study was to develop a typology of the range of peripheral nervous system (PNS) disorders. This typology serves as a valuable tool for clinicians in their daily practice and also provides a foundation for future research in comparative and mechanistic investigations. To accomplish this

objective, we conducted a comprehensive literature review and present the outcomes as a research synthesis.

Aim

A literature study was conducted in order to identify and summarize the characteristics and meta-analysis of existing studies in this particular field.

Material and methods

A study conducted on 28 September 2023 was aimed to identify relevant literature. The PubMed and Medline databases were searched using different variations of two primary keywords: “melanoma” and “paraneoplastic syndromes”. Additionally, other variations of the aforementioned key terms, namely “PNS” and “MM”, have been used in our study. The selected publication dates encompassed the time period from 1986 to 2023. A total of 392 papers, including abstracts, original texts, and case reports, were identified. A total of 270 publications were

Address for correspondence: Hubert Arasiewicz MD, PhD, Department of Dermatology and Vascular Anomalies, John Paul II Centre of Paediatrics, 3 Gabrieli Zapolskiej St, 41-218 Sosnowiec, Poland, phone: +48 608 535 285, e-mail: hubert.arasiewicz@gmail.com

Received: 23.10.2023, **accepted:** 2.02.2024, **online publication:** 30.06.2024.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License (<http://creativecommons.org/licenses/by-nc-sa/4.0/>)

Table 1. The study flowchart

Identification of studies via databases	
Records identified from PubMed and Medline databases (<i>n</i> = 392)	Records removed before screening: duplicate records, records removed for other reasons (not PNS patients, not melanoma patents) (<i>n</i> = 270)
Record screened (<i>n</i> = 122)	
Full texts assessed (<i>n</i> = 57)	
Total number of detailed cases in all included papers (<i>n</i> = 59)	

removed from the analysis. The literature review only comprised original publications written solely in the English language, focusing on a research population consisting of individuals with melanoma and paraneoplastic syndromes (PNS). The review included case series, case reports, and experimental randomized controlled trials. The analysis focused on the general characteristics of the patient with melanoma with associated paraneoplastic syndrome (PNS) (age at the time of diagnosis, sex, location of melanoma, stage of malignancy, metastasis, cancer treatment, recurrence, predilection, timing of PNS).

A total of 59 patients diagnosed with paraneoplastic syndrome (PNS) associated with malignant melanoma were included in the study. Table 1 visually depicts the study selection process. The earliest recorded instance of melanoma with associated paraneoplastic syndrome (PNS) dates back to 1986. The literature incorporated in this review consists of a total of 57 original papers [1–57] (Tables 2, 3).

Results

We did not find any review paper that compiles the topic of melanoma-associated PNS. Our literature search yielded only papers reporting solitary cases (57 papers reporting 59 PNS cases associated with melanoma) (Table 2). Table 3 compiles the core clinical features of the patients. Of the 59 patients with melanoma-associated PNS, 34 were male (57.63%) and 25 were female (42.37%). The most common localization of melanoma was extremities (16/59, or 27.12% of all reported PNS cases). There were reports of twenty-six distinct PNS entities (Table 2). Melanoma-associated retinopathy (MAR) syndrome was the most reported PNS (25/59 cases, 42.37% of all reported PNS cases). The median age of the patients at the time of PNS diagnosis was 63.07 years (range: 34–83 years). In most cases (44/59 patients), PNS was diagnosed either concurrently or after the melanoma, considering the timing of PNS manifestation. Resolution of paraneoplastic syndrome after melanoma treatment was observed in 42.59% of the cases.

Discussion

Paraneoplastic syndromes (PNS) are tumour-associated manifestations that occur outside the primary tumour

site and are not caused by the spread of cancer cells to other parts of the body [58, 59]. Paraneoplastic syndromes (PNS) are present in a significant proportion of individuals with tumours and can predominantly impact various organ systems such as the neuromuscular/musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, endocrine, or renal systems [59]. The literature has identified several systemic symptoms of these diseases, such as thrombocytopenia, nephrotic syndrome, dermatomyositis, and opsoclonus-myoclonus syndrome. Furthermore, in certain instances, PNS might serve as the initial or most notable indication of an underlying cancer; therefore, promptly identifying them can assist in the investigation of an undetected malignancy. From a pathophysiologic perspective, the majority of paraneoplastic syndrome (PNS) disorders can be attributed to either endocrine phenomena caused by biomolecules produced by tumours, or immunological mechanisms mediated by autoimmunity [60, 61]. Visceral tumours can affect the skin directly or indirectly. Direct involvement refers to the presence of tumour cells within the skin. This can happen either through direct expansion or by the metastasis of the tumour. Almost all types of internal cancer have the ability to spread to the skin through metastasis. The skin can be affected indirectly by visceral tumours, leading to various distinct inflammatory, proliferative, metabolic, and neoplastic changes even in the presence of actual tumour cells. This diverse group of disorders includes inherited syndromes associated with skin manifestations and an increased incidence of systemic neoplasia, cutaneous changes resulting from hormone secretion by tumours, and a wide spectrum of proliferative and inflammatory disorders reported in patients with internal malignancies. Curth’s postulates are a well-known set of clinical criteria that were created to help evaluate the temporal relationship between an underlying malignancy and a specific dermatological condition. The criteria are as follows: 1) The malignancy and the skin disease are of concurrent onset. 2) The malignancy and the skin disease run a parallel course. Successful treatment of the tumour leads to regression of the skin disease, and recurrence of the tumour leads to a return of cutaneous signs and symptoms. 3) The relationship between the skin disease and the malignancy is uniform. A specific tumour cell type or site is associated with a characteristic cutaneous eruption. 4) Based on sound case-control studies, a statisti-

Table 2. Characteristics of patients with melanoma associated with paraneoplastic syndromes

Ref.	PNS	Sex	Age of PNS symptoms	Localization of melanoma	Metastasis/recurrence	Timing of PNS	Melanoma/PNS treatment	Resolution of PNS
Paraneoplastic syndromes of the nervous system								
1	Cerebellar degeneration with opsoclonus myoclonus	F	52	Vagina	Yes/Yes	After	Surgery	No (patient died)
2	Opsoclonus-myoclonus syndrome	F	36	N/A	Yes/No	Before	Patient died before treatment	No (patient died)
3	Opsoclonus-myoclonus syndrome	F	69	Left nasal cavity	No/No	Before	Surgery	No (patient died)
4	Progressive ataxia and dysidiadochokinesia	M	58	Lower back	Yes/Yes	After	BRAF targeted therapy, prednisone, intravenous immunoglobulins	Yes
5	Paraneoplastic cerebellar degeneration (PCD)	M	61	N/A	Yes/No	Before	Trametinib (MEK inhibitor, prednisolone)	Yes
6	Guillain-Barré syndrome	M	68	N/A	Yes/No	Before	N/A	No (patient died)
7	Opsoclonus-myoclonus syndrome	F	59	Vagina	Yes/No	After	Oral prednisolone, family declined further therapeutic intervention	No (patient died)
8	Paraneoplastic limbic encephalitis	F	60	Back	Yes/No	After	Surgery, radiotherapy, oral prednisolone, immunoglobulins	No (patient died)
9	Paraneoplastic cerebellar degeneration (PCD)	M	58	Uveal melanoma	Yes/No	After	Brachytherapy, chemotherapy	No (patient died)
10	Limbic encephalitis	M	64	Calf	Yes/No	After	Vemurafenib, pembrolizumab	No (patient died)
Ophthalmologic manifestations of paraneoplastic syndromes								
11	Melanoma-associated retinopathy (MAR) syndrome	F	58	Choroidal melanoma	Yes/No	After	Dacarbazine and dasatinib, and immunotherapy (interleukin-2)	No (patient died)
12	Melanoma-associated retinopathy (MAR) syndrome	M	68	Choroidal melanoma	No/Yes	After	Stereotactic orbital radiation, modified enucleation with en bloc resection of the eye	Yes
13	Melanoma-associated retinopathy (MAR) syndrome	M	59	Back	Yes/No	After	Palliative resection and chemotherapy	Yes
13	Melanoma-associated retinopathy (MAR) syndrome	M	56	Choroidal melanoma	Yes/No	After	Palliative chemotherapy	No (patient died)
14	Melanoma-associated retinopathy (MAR) syndrome	M	63	Conjunctival melanoma	Yes/Yes	Simultaneously	Surgery	Yes
15	Bilateral diffuse uveal melanocytic proliferation (B-DUMP)	F	70	N/A	No/No	Simultaneously	Plasmapheresis, oral steroids, surgery	No

Table 2. Cont.

Ref.	PNS	Sex	Age of PNS symptoms	Localization of melanoma	Metastasis/recurrence	Timing of PNS	Melanoma/PNS treatment	Resolution of PNS
16	Melanoma-associated retinopathy (MAR) syndrome	M	44	Left leg	Yes/No	After	Surgery, prednisone, acetazolamide, flurbiprofen	Yes
17	Melanoma-associated retinopathy (MAR) syndrome	F	41	N/A	Yes/No	After	Surgery	Improvement
18	Melanoma-associated retinopathy (MAR) syndrome	M	58	Left shoulder	Yes/No	After	Interleukin-2, surgery, dacarbazine	Slight improvement
19	Melanoma-associated retinopathy (MAR) syndrome	M	44	N/A	Yes/No	After	Dabrafenib (B-RAF inhibitor) and trametinib (MEK inhibitor)	Slight improvement
20	Melanoma-associated retinopathy (MAR) syndrome	M	66	N/A	Yes/No	Before	Surgery, chemotherapy	Yes
21	Paraneoplastic optic neuropathy (PON)	F	67	N/A	Yes/No	Before	Surgery, low-dose prednisone, and monthly plasmapheresis	Slight improvement
22	Melanoma-associated retinopathy (MAR) syndrome	F	62	choroidal melanoma	Yes/No	After	Enucleation	No (patient died)
23	Melanoma-associated retinopathy (MAR) syndrome	M	74	Left upper arm	Yes/No	After	Surgery	N/A
24	Melanoma-associated retinopathy (MAR) syndrome	F	55	N/A	Yes/No	After	Pembrolizumab and dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor)	No (patient died)
25	Melanoma-associated retinopathy (MAR) syndrome	F	70	Choroidal melanoma	Yes/No	After	Ipilimumab	No
26	Neuromyelitis optica spectrum disorders (NMOSDs)	F	61	N/A	Yes/No	Before	Oral prednisolone, nivolumab, paclitaxel, carboplatin	No (patient died)
27	Melanoma-associated retinopathy (MAR) syndrome	M	77	Nasal cavity	No/No	Before	Surgery	Yes
28	Melanoma-associated retinopathy (MAR) syndrome	F	46	Right thigh	No/No	After	Surgery	N/A
28	Melanoma-associated retinopathy (MAR) syndrome	M	46	Back	No/No	After	Surgery	N/A

Table 2. Cont.

Ref.	PNS	Sex	Age of PNS symptoms	Localization of melanoma	Metastasis/recurrence	Timing of PNS	Melanoma/PNS treatment	Resolution of PNS
29	Melanoma-associated retinopathy (MAR) syndrome	M	73	N/A	Yes/No	Before	Chemotherapy and radiation	No (patient died)
30	Melanoma-associated retinopathy (MAR) syndrome	M	55	Small intestinal melanoma	Yes/No	Before	Surgery	No (patient died)
31	Melanoma-associated retinopathy (MAR) syndrome	M	61	Foot	Yes/No	After	Chemotherapy	No
32	Melanoma-associated retinopathy (MAR) syndrome	M	74	Choroidal melanoma	Yes/No	Before	No treatment	No (patient died)
33	Melanoma-associated retinopathy (MAR) syndrome	M	74	Left arm	Yes/No	After	Pembrolizumab	Yes
34	Melanoma-associated retinopathy (MAR) syndrome	M	68	Right ankle	Yes/No	After	Prednisone	Improvement
35	Paraneoplastic ophthalmoplegia	F	68	Left foot	Yes/No	After	Immunotherapy, intravenous immunoglobulin, dexamethasone	Yes
Rheumatic manifestations of paraneoplastic syndromes								
36	Adult onset Still's disease (AOSD)	F	50	N/A	Yes/No	Before	Vemurafenib, prednisone	Yes
37	Polymyalgia rheumatica	M	63	Interscapular region	Yes/No	After	Pembrolizumab, prednisone	Yes
38	Dermatomyositis	M	70	Right foot	Yes/No	After	Dacarbazine cisplatin, fotemustine	No (patient died)
39	Eosinophilic fasciitis	F	67	Choroidal melanoma	Yes/Yes	After	Prednisone, radiotherapy	Yes
40	Eosinophilic fasciitis	F	72	Thigh	No/Yes	Simultaneously	Surgery, prednisone	Yes
41	Dermatomyositis	F	34	Right shoulder	Yes/No	Before	Surgery, radiotherapy	Yes
42	Jo-1 positive paraneoplastic systemic sclerosis	F	40	N/A	Yes/No	After	Surgery	No (patient died)
43	Dermatomyositis	M	44	Left thigh	Yes/No	After	Chemotherapy and immunotherapy, radiotherapy	Yes
Haematologic manifestations of paraneoplastic syndromes								
44	Paraneoplastic neutrophilic leukemoid reaction (PNLR)	F	43	Left thigh	Yes/No	After	Dabrafenib, nivolumab, vemurafenib, cobimetinib	No (patient died)
45	Paraneoplastic eosinophilia	F	64	Right knee	Yes/Yes	After	Vinblastine, carboplatin, vindesine, DTIC, vincristine and fotemustine	No (patient died)

Table 2. Cont.

Ref.	PNS	Sex	Age of PNS symptoms	Localization of melanoma	Metastasis/recurrence	Timing of PNS	Melanoma/PNS treatment	Resolution of PNS
46	Paraneoplastic hyperleukocytosis (PH)	F	72	Upper leg	Yes/No	After	Ipilimumab and nivolumab, radiotherapy	Yes
Paraneoplastic cutaneous manifestations								
47	Eruptive melanocytic nevi (EMN)	M	83	Back	Yes/No	After	Nivolumab	No reduction in number and size, but no increase in number either
48	Multiple trichilemmal cysts	M	57	N/A	Yes/No	Simultaneously	Surgery	Yes
49	Paraneoplastic pemphigus	M	72	Right shoulder	Yes/No	After	Surgery	Yes
50	Sweet's syndrome	F	77	Nasal cavity	Yes/No	After	Surgery, ipilimumab, radiotherapy, prednisolone	No (patient died)
51	Leser-Trélat Sign (LTS)	M	82	Right ear	Yes/No	After	Surgery, dacarbazine	N/A
52	Leser-Trélat Sign (LTS)	F	80	Right flank	No/No	Simultaneously	Surgery	Yes
53	Subacute cutaneous lupus erythematosus (SCLE)	M	52	Abdomen	No/No	Simultaneously	Surgery, hydroxychloroquine	Yes
Paraneoplastic syndromes affecting other organ systems								
54	Granulomatous cardiomyopathy	M	64	N/A	Yes/No	After	Immune check-point inhibitor therapy (ICI, prednisone)	Yes
55	Hypertrophic osteoarthropathy (HOA)	F	45	Upper back	Yes/No	Before	Surgery, chemotherapy, radiotherapy, steroids	Improvement
56	Membranous glomerulonephritis (MG)	M	61	Right side	Yes/No	Simultaneously	Surgery, chemotherapy	Yes
57	Paraneoplastic acral vascular syndrome	M	60	N/A	Yes/No	After	Nivolumab, ipilimumab, prednisolone	No (patient died)

Ref. – References list number, F – female, M – male, N/A – information not available, PNS – paraneoplastic syndrome, Recurrence – local relapse, Metastasis – distant relapse. Timing of PNS. Before: PNS diagnosis precedes tumour diagnosis; simultaneously: PNS present at the time of tumour diagnosis; after: PNS diagnosis after tumour diagnosis.

cally significant association exists between the malignancy and a specific cutaneous disease. and/or 5) A genetic association exists between the malignancy and a specific cutaneous disease. Not all criteria must be met to postulate a relationship between a skin disease and an underlying malignancy [62]. While the skin is commonly affected by paraneoplastic syndrome (PNS) disorders [62, 63], PNS have been rather rarely reported in the course of skin neoplasms, even in relation to the biologically more aggressive ones, like malignant melanoma and Merkel cell carcinoma [64, 65].

Melanoma-associated retinopathy (MAR) was the PNS most frequently reported in patients with melanoma. In MAR syndrome, ocular symptoms usually manifest years after the diagnosis of skin melanoma, and the onset of

MAR may herald the presence of metastatic disease. Melanoma-associated retinopathy syndrome is more frequent in males and typically presents as night blindness of acute onset. Additional symptoms may encompass photopsia, flashing, and peripheral field impairment [66].

There is a lack of consensus about the management of melanoma paraneoplastic retinopathies. Generally, the utilization of steroids and immunosuppressive medications, plasmapheresis, or intravenous immunoglobulins is not beneficial. Some reports say that steroids can make eye symptoms worse, but another report says that the paraneoplastic autoimmune response is an immune system defence against the spread of melanoma, and that using an immunosuppressive treatment may take away

Table 3. Compilation of the clinical features of all cases

Melanoma		Total (N = 59)
Sex, n (%)	Male	34 (57.63)
	Female	25 (42.37)
Age of PNS onset (average)[range]	(63.07) [34–83]	
Localization, n (%)	Head/neck	15 (25.42)
	Trunk	8 (13.56)
	Extremities	16 (27.12)
	Genitals	2 (3.39)
	Others	1 (1.69)
	N/A	16 (27.12)
PNS, n (%)	Melanoma-associated retinopathy (MAR) syndrome	25 (42.37)
	Dermatomyositis	3 (5.08)
	Limbic encephalitis	2 (3.39)
	Leser-Trélat sign (LTS)	2 (3.39)
	Opsoclonus-myoclonus syndrome	3 (5.08)
	Paraneoplastic cerebellar degeneration (PCD)	3 (5.08)
	Eosinophilic fasciitis	2 (3.39)
	Other	19 (32.20)
Timing of PNS, n (%)	Before	15 (25.42)
	After	37 (62.71)
	Simultaneously	7 (11.86)
Recurrence, n (%)	Yes	7 (11.86)
	No	52 (88.13)
Metastases, n (%)	Yes	50 (84.74)
	No	9 (15.25)
Resolution, n (%)	Yes	23 (42.59)
	No	27 (50)
	N/A	4 (7.41)

N (%) – number of cases and % of corresponding cases with available information.

N/A – not available, PNS: Localization – localization of the primary neoplasm. Timing of PNS – time point of PNS diagnosis relative to the diagnosis of skin cancer. Recurrence – local tumour recurrence after treatment. Resolution – resolution of paraneoplastic syndrome after skin cancer treatment.

this protection for the patient [32]. Conducting larger therapy studies is highly challenging due to the limited number of people affected by these illnesses [67, 68].

The management of MAR-induced vision impairment has proven generally inefficacious. Nevertheless, on certain occasions, the utilization of a combination of cytoreductive surgery, x-irradiation, intravenous corticosteroids, plasma exchange, and IVIg has demonstrated some advantageous effects.

According to Guy *et al.* study, IVIg has demonstrated efficacy in treating paraneoplastic vision loss associated with MAR syndrome in two out of three individuals [69]. It has proven beneficial in treating various autoimmune neurologic diseases, such as Guillain-Barré syndrome, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, multiple

sclerosis, dermatomyositis, and immunologic ophthalmologic conditions like ocular cicatricial pemphigoid, refractory uveitis, and linear IgA bullous disease limited to the eye [70–76].

Opsoclonus is characterized by the occurrence of spontaneous, irregular, and high-amplitude coordinated eye movements in all directions of vision, without any pauses between the movements. Three distinct clinical contexts detect paraneoplastic opsoclonus-myoclonus syndrome (POMS): (i) paediatric patients diagnosed with neuroblastoma; (ii) adult female patients with Ri-Ab, typically associated with breast cancer; and (iii) adult patients with small-cell lung carcinoma as the predominant tumour type. Other tumours, like melanoma have been linked to individual case reports [77].

Researchers have not yet fully understood the underlying mechanisms of the POMS. The observed clinical distinctions between POMS and idiopathic opsoclonus-myoclonus indicate varying pathways based on the triggering stimulus [78]. POMS is thought to occur due to an immunological response triggered by molecular mimicry between the tumour and a specific set of neurons in the central nervous system [79, 80]. Nevertheless, it is not uncommon for antineuronal antibodies to be absent as evidenced by a significant number of patients, especially in previously documented cases of melanoma-associated POMS [80–82]. Paraneoplastic neurological syndromes encompass a range of conditions, such as paraneoplastic cerebellar degeneration (PCD), paraneoplastic limbic encephalitis, subacute sensory neuropathy, paraneoplastic opsoclonus-myoclonus, and Lambert-Eaton myasthenic syndrome [83]. Paraneoplastic degenerative cerebellar ataxia refers to the sudden or gradual loss of coordination in a patient who has been diagnosed with cancer within the past 5 years, or who has particular onconeural antibodies present [84]. The correlation between PCD and malignant melanoma has previously been linked to carbonic anhydrase-related protein VIII.

There have been a few reports of patients who have malignant melanoma (MM) in coexistence with or heralding the clinical manifestations of dermatomyositis. Dermatomyositis can either precede, coincide with, or be diagnosed after the development of MM.

Regardless of the time of diagnosis, researchers have shown that MM staging is the most significant prognostic factor identified [85]. Although rare, there is an increasingly poor prognosis associated with the presence of dermatomyositis in patients with advanced MM. Dermatomyositis activity may serve as an indicator of disease progression and activity associated with MM [24].

There is a considerable controversy as to whether the presence of multiple trichilemmal cysts with melanoma can be a paraneoplastic syndrome. The casuistic report on the presence of multiple trichilemmal cysts with melanoma, as presented in the article by Savarese *et al.*, necessitates verification and more observations. The literature does not document any previous correlation between trichilemmal cysts and neoplasia. However, in Cowden syndrome, several trichilemmomas have been linked to the development of neoplasms such as melanoma [48]. Perrotta *et al.* [37] reported a case of polymyalgia rheumatica in a male patient with three distinct neoplasms who was treated with pembrolizumab. They suggested that polymyalgia rheumatica could be caused by the neoplasms (not specifically melanoma) or could be a side effect of pembrolizumab treatment. The treatment with pembrolizumab triggered the patient's symptoms a few months after it was started. Researchers have described immune-related adverse events induced by cancer immunotherapy in various clinical settings. The uniqueness of this case lies in the patient's occurrence

of three distinct neoplasms, including a particularly uncommon instance of male breast cancer. It is up for debate, nevertheless, whether the pembrolizumab or the neoplasms themselves caused the start of polymyalgia rheumatica syndrome.

Gambichler *et al.* [57] documented a case of abruptly progressing digital ischemia in an older patient with malignant melanoma. Paraneoplastic acral vascular syndrome (PAVS) is an uncommon occurrence that is seen in individuals with adenocarcinomas and other types of malignancies. Nevertheless, there remains a subject of debate regarding the potential involvement of immune checkpoint inhibition in the pathogenesis of PAVS in individuals with malignancies. In this specific instance, PAVS could be classified as either a paraneoplastic syndrome or a consequence of immune checkpoint inhibitor medication.

Descriptions of cases of melanoma-associated PNS are sparsely reported in the medical literature. This is in distinct contrast with the high incidence of melanoma, at least among Caucasians. Future studies should inquire whether melanoma-associated PNS are truly rare events or whether they are simply underrecognized and consequently underreported conditions.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Hauspy J, Nevin A, Harley I, et al. Paraneoplastic syndrome in vaginal melanoma: a case report and review of the literature. *Int J Gynecol Cancer* 2007; 17: 1159-63.
2. Mondragón JD, Jiménez-Zarazúa O, Vélez-Ramírez LN, et al. Paraneoplastic opsoclonus-myoclonus syndrome secondary to melanoma metastasis form occult primary cancer. *Case Rep Neurol* 2019; 11: 66-79.
3. Dresco F, Aubin F, Deveza E, et al. Paraneoplastic opsoclonus-myoclonus syndrome preceding a mucosal malignant melanoma. *Acta Derm Venereol* 2019; 99: 337-8.
4. Lee SF, Atkinson V. A case of acute paraneoplastic neurological syndrome in BRAF mutant metastatic melanoma. *Melanoma Res* 2016; 26: 425-8.
5. Jiménez-Zarazúa O, Vélez-Ramírez LN, Alcocer-León M, et al. Paraneoplastic cerebellar degeneration secondary to BRAF mutant melanoma metastasis from an occult primary cancer. *Case Rep Oncol* 2020; 13: 633-42.
6. Rovere RK, Pires de Souza ME, Hilgert SF, et al. Melanoma metastasis to the gastric mucosa preceded by guillain-bar-

- ré as a paraneoplastic syndrome. *Gastrointest Cancer Res* 2013; 6: 150-1.
7. Jung KY, Youn J, Chung CS. Opsoclonus-myoclonus syndrome in an adult with malignant melanoma. *J Neurol* 2006; 253: 942-3.
 8. Becquart C, Ryckewaert G, Desmedt E, et al. Encéphalite limbique : une nouvelle manifestation auto-immune paranéoplasique associée au mélanome métastatique ? [Limbic encephalitis: a new paraneoplastic auto-immune manifestation associated with metastatic melanoma?]. *Ann Dermatol Venereol* 2013; 140: 278-81.
 9. Valpione S, Zoccarato M, Parrozzani R, et al. Paraneoplastic cerebellar degeneration with anti-Yo antibodies associated with metastatic uveal melanoma. *J Neurol Sci*. 2013; 335: 210-2.
 10. Salam S, Lavin T, Turan A. Limbic encephalitis following immunotherapy against metastatic malignant melanoma. *BMJ Case Rep* 2016; 2016: bcr2016215012.
 11. Williams SL, McDonald HR, Jumper JM, et al. Paraneoplastic vitelliform retinopathy in a patient with treated choroidal melanoma. *Retin Cases Brief Rep* 2014; 8: 269-72.
 12. Nagiel A, Rootman DB, McCannel TA. Paraneoplastic vitelliform maculopathy in the setting of choroidal melanoma: evolution over one year. *Retin Cases Brief Rep* 2017; 11 Suppl 1: S7-10.
 13. Sotodeh M, Paridaens D, Keunen J, et al. Paraneoplastic vitelliform retinopathy associated with cutaneous or uveal melanoma and metastases. *Klin Monbl Augenheilkd* 2005; 222: 910-4.
 14. Evoy F, Lafortune J. First case of melanoma-associated retinopathy with conjunctival melanoma. *Can J Ophthalmol* 2020; 55: e153-5.
 15. Navarrete-Dechent C, Monnier J, Marghoob NG, et al. Bilateral diffuse uveal melanocytic proliferation with multifocal diffuse integumentary melanocytic proliferation paraneoplastic syndrome: a case report. *Australas J Dermatol* 2021; 62: 386-9.
 16. Kellner U, Bornfeld N, Foerster MH. Severe course of cutaneous melanoma associated paraneoplastic retinopathy. *Br J Ophthalmol* 1995; 79: 746-52.
 17. Meier PG, Ambresin A, Thirkill CE, et al. Paraneoplastic vitelliform retinopathy secondary to metastatic melanoma. *Klin Monbl Augenheilkd* 2015; 232: 587-9.
 18. Krema H, Simpson R, Altomare F, Ebadi M. Paraneoplastic vitelliform retinopathy in metastatic cutaneous melanoma. *Retin Cases Brief Rep* 2010; 4: 246-50.
 19. Rahimi M, Navajas EV, Sarraf D. Paraneoplastic vitelliform maculopathy associated with metastatic melanoma. *Retin Cases Brief Rep* 2018; 12 Suppl 1: S102-4.
 20. Kiratli H, Thirkill CE, Bilgiç S, et al. Paraneoplastic retinopathy associated with metastatic cutaneous melanoma of unknown primary site. *Eye (Lond)* 1997; 11: 889-92.
 21. Schoenberger SD, Kim SJ, Lavin P. Paraneoplastic optic neuropathy from cutaneous melanoma detected by positron emission tomographic and computed tomographic scanning. *Arch Ophthalmol* 2012; 130: 1223-5.
 22. Nieuwendijk TJ, Hooymans JM. Paraneoplastic vitelliform retinopathy associated with metastatic choroidal melanoma. *Eye (Lond)* 2007; 21: 1436-7.
 23. Heberton M, Azher T, Council ML, Khanna S. Metastatic cutaneous melanoma presenting with melanoma-associated retinopathy. *Dermatol Surg* 2019; 45: 606-7.
 24. Tian JJ, Coupland S, Karanjia R, Sadun AA. Melanoma-associated retinopathy 28 years after diagnosis. *JAMA Ophthalmol* 2017; 135: 1276-77.
 25. Audemard A, de Raucourt S, Miocque S, et al. Melanoma-associated retinopathy treated with ipilimumab therapy. *Dermatology* 2013; 227: 146-9.
 26. Morimoto T, Hayashida S, Yamasaki K, et al. Paraneoplastic neuromyelitis optica spectrum disorder associated with malignant melanoma: a case report. *Thorac Cancer* 2021; 12: 1775-9.
 27. Machida S, Ohguro H, Tateda M, et al. Melanoma-associated retinopathy associated with intranasal melanoma. *Doc Ophthalmol* 2011; 122: 191-7.
 28. Weinstein JM, Kelman SE, Bresnick GH, Kornguth SE. Paraneoplastic retinopathy associated with antiretinal bipolar cell antibodies in cutaneous malignant melanoma. *Ophthalmology* 1994; 101: 1236-43.
 29. Khurana RN, Wieland MR, Boldrey EE, et al. Vitelliform retinopathy in metastatic cutaneous melanoma with choroidal involvement. *Arch Ophthalmol* 2011; 129: 1498-9.
 30. Rappoport D, Leiba H. Presumed melanoma-associated retinopathy (MAR): a presenting sign of primary small intestinal melanoma? *Int Ophthalmol* 2012; 32: 387-91.
 31. Potter MJ, Thirkill CE, Dam OM, et al. Clinical and immunocytochemical findings in a case of melanoma-associated retinopathy. *Ophthalmology* 1999; 106: 2121-5.
 32. Okel BB, Thirkill CE, Anderson K. An unusual case of melanoma-associated retinopathy. *Ocul Immunol Inflamm* 1995; 3: 121-8.
 33. Khaddour K, Khanna S, Ansstas M, et al. Normalization of electroretinogram and symptom resolution of melanoma-associated retinopathy with negative autoantibodies after treatment with programmed death-1 (PD-1) inhibitors for metastatic melanoma. *Cancer Immunol Immunother* 2021; 70: 2497-502.
 34. Ng CC, Alsberge JB, Qian Y, et al. Vogt-Koyanagi-Harada-like uveitis followed by melanoma-associated retinopathy with focal chorioretinal atrophy and choroidal neovascularization in a patient with metastatic cutaneous melanoma. *Retin Cases Brief Rep* 2023; 17: 18-22.
 35. Kloos L, Sillevs Smitt P, Ang CW, et al. Paraneoplastic ophthalmoplegia and subacute motor axonal neuropathy associated with anti-GQ1b antibodies in a patient with malignant melanoma. *J Neurol Neurosurg Psychiatry* 2003; 74: 507-9.
 36. Liozon E, Ly KH, Vidal-Cathala E, Fauchais AL. Pseudomaladie de Still et néoplasie : une observation de mélanome et revue de la littérature [Adult-onset Still's disease as a manifestation of malignancy: report of a patient with melanoma and literature review]. *Rev Med Interne* 2014; 35: 60-4.
 37. Perrotta FM, Scriffignano S, Fatica M, et al. Case report of polymyalgia rheumatica in a male patient with three different neoplasms treated with pembrolizumab. *Reumatismo* 2020; 72: 178-81.
 38. Jouary T, Gracia C, Lalanne N, et al. Rapidly lethal dermatomyositis associated with metastatic melanoma. *J Eur Acad Dermatol Venereol* 2008; 22: 399-401.
 39. Veyssier-Belot C, Zuech P, Lumbroso-Le Rouic L, et al. Fasciite à éosinophiles révélant l'extension métastatique d'un mélanome de la choroïde : un syndrome paranéoplasique [Eosinophilic fasciitis and metastatic choroïdal melanoma: a paraneoplastic syndrome?]. *Rev Med Interne* 2008; 29: 1013-6.

40. Rea A, Anderson A, Moshiri A, et al. Eosinophilic fasciitis as a paraneoplastic syndrome in melanoma. *JAAD Case Rep* 2021; 17: 49-51.
41. Tu J, Von Nida J. Metastatic malignant melanoma and dermatomyositis: a paraneoplastic phenomenon. *Australas J Dermatol* 2011; 52: e7-10.
42. Thoele A, Schmid HP, Figl R, et al. Jo-1 positive paraneoplastic systemic sclerosis in a patient with metastatic melanoma. *Eur J Dermatol* 2006; 16: 428-30.
43. Schiller M, Böhm M, Hensen P, et al. Dermatomyositis associated with malignant melanoma—a marker of poor prognosis? *J Am Acad Dermatol* 2006; 54: 221-6.
44. Fredeau L, Bohelay G, Shourick J, et al. Paraneoplastic neutrophilic leukaemoid reaction in a patient with melanoma: association between tumour volume and leucocytosis. *Br J Dermatol* 2020; 183: 579-80.
45. Rule SA, Waterhouse P, Costello C, Retsas S. Paraneoplastic eosinophilia in malignant melanoma. *J R Soc Med* 1993; 86: 295.
46. Gambichler T, Stockfleth E, Susok L. Paraneoplastic hyperleucocytosis in a melanoma patient after initiation of ipilimumab and nivolumab combination therapy. *J Immunother Cancer* 2018; 6: 113.
47. De Giorgi V, Gemignani A, Scarfi F, et al. Eruptive melanocytic nevi in a patient with amelanotic melanoma: a paraneoplastic phenomenon? *Melanoma Res* 2022; 32: 63-6.
48. Savarese I, Grazzini M, Gori A, et al. Trichilemmal cysts in metastatic melanoma: a case report. *Exp Oncol* 2017; 39: 86-7.
49. Schaeppi H, Bauer JW, Hametner R, et al. A localized variant of paraneoplastic pemphigus: acantholysis associated with malignant melanoma. *Br J Dermatol* 2001; 144: 1249-54.
50. Pintova S, Sidhu H, Friedlander PA, Holcombe RF. Sweet's syndrome in a patient with metastatic melanoma after ipilimumab therapy. *Melanoma Res* 2013; 23: 498-501.
51. Siedek V, Schuh T, Wollenberg A. Leser-Trélat sign in metastasized malignant melanoma. *Eur Arch Otorhinolaryngol* 2009; 266: 297-9.
52. Gori N, Esposito I, Del Regno L, et al. Leser-Trélat sign as a rare manifestation of cutaneous melanoma. *Dermatol Rep* 2020; 12: 8665.
53. Hirner J. Subacute cutaneous lupus erythematosus with a possible paraneoplastic association with melanoma. *BMJ Case Rep* 2019; 12: e230558.
54. Kolominsky J, Poklepovic A, Syed A, et al. Granulomatous cardiomyopathy presenting as a paraneoplastic syndrome in metastatic melanoma. *CJC Open* 2023; 5: 713-6.
55. Thompson MA, Warner NB, Hwu WJ. Hypertrophic osteoarthropathy associated with metastatic melanoma. *Melanoma Res* 2005; 15: 559-61.
56. Sultan-Bichat N, Vuible V, Winckel A, et al. Glomérulonéphrite extramembraneuse paranéoplasique au cours d'un mélanome [Membranous glomerulonephritis as a paraneoplastic manifestation of melanoma]. *Ann Dermatol Venerol* 2011; 138: 46-9.
57. Gambichler T, Strutzmann S, Tannappel A, Susok L. Paraneoplastic acral vascular syndrome in a patient with metastatic melanoma under immune checkpoint blockade. *BMC Cancer* 2017; 17: 327.
58. Hobbs CB, Miller AL. Review of endocrine syndromes associated with tumours of non-endocrine origin. *J Clin Pathol* 1966; 19: 119-27.
59. Bilynsky BT, Dzhus MB, Litvinyak RI. The conceptual and clinical problems of paraneoplastic syndrome in oncology and internal medicine. *Exp. Oncol* 2015; 37: 82-8.
60. Dimitriadis GK, Angelousi A., Weickert MO, et al. Paraneoplastic endocrine syndromes. *Endocr Relat Cancer* 2017; 24: R173-90.
61. Maverakis E, Goodarzi H, Wehrli LN, et al. The etiology of paraneoplastic autoimmunity. *Clin Rev Allergy Immunol* 2012; 42: 135-44.
62. Thiers BH, Sahn RE, Callen JP. Cutaneous manifestations of internal malignancy. *CA Cancer J Clin* 2009; 59: 73-98.
63. Ehst BD, Minzer-Conzetti K, Swerdlin A, Devere TS. Cutaneous manifestations of internal malignancy. *Curr Probl Surg* 2010; 47: 384-445.
64. Vyas R, Selph J, Gerstenblith MR. Cutaneous manifestations associated with melanoma. *Semin Oncol* 2016; 43: 384-9.
65. Iyer JG, Parvathaneni K, Bhatia S, et al. Paraneoplastic syndromes (PNS) associated with merkel cell carcinoma (MCC): a case series of 8 patients highlighting different clinical manifestations. *J Am Acad Derm* 2016; 75: 541-7.
66. Jacobson DM. Paraneoplastic diseases of neuro-ophthalmology interest. In: Walsh & Hoyt's Clinical Neuro-ophthalmology. Miller NR, Newman NJ, eds. Baltimore: Williams & Wilkins 1998; 2497-551.
67. Keltner JL, Thirkill CE, Yip PT. Clinical and immunologic characteristic of melanoma-associated retinopathy syndrome: eleven new cases and a review of 51 previously published cases. *J Neuroophthalmol* 2001; 21: 173-87.
68. Chan C, O'Day J. Melanoma-associated retinopathy: does autoimmunity prolong survival? *Clin Experiment Ophthalmol* 2001; 29: 235-8.
69. Guy J, Aptsiauri N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin: report of 3 cases. *Arch Ophthalmol* 1999; 117: 471-7.
70. Dalakas MC. The use of intravenous immunoglobulin for neurologic diseases. *Neurology* 1998; 51 (6 suppl 5): S1-45.
71. Qureshi AI, Choudhry MA, Akbar MS, et al. Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. *Neurology* 1999; 52: 629-32.
72. Visser LH, Schmitz PI, Meulstee J, et al. Prognostic factors of Guillain-Barre syndrome after intravenous immunoglobulin or plasma exchange. Dutch Guillain-Barré Study Group. *Neurology* 1999; 53: 598-604.
73. Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; 55: 1256-62.
74. Foster CS, Ahmed AR. Intravenous immunoglobulin therapy for ocular cicatricial pemphigoid: a preliminary study. *Ophthalmology* 1999; 106: 2136-43.
75. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. *Am J Ophthalmol* 1999; 127: 545-9.
76. Letko E, Bhol K, Foster CS, et al. Linear IgA bullous disease limited to the eye: a diagnostic dilemma: response to intravenous immunoglobulin therapy. *Ophthalmology* 2000; 107: 1524-8.
77. Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. *Orphanet J Rare Dis* 2007; 2: 22-30.
78. Honnorat J. New findings in adult opsoclonus-myoclonus syndrome. *JAMA Neurol* 2016; 73: 381-2.
79. Armangué T, Sabater L, Torres-Vega E, et al. Clinical and immunological features of opsoclonus-myoclonus syndrome in the era of neuronal cell surface antibodies. *JAMA Neurol* 2016; 73: 417-24.

80. Honnorat J. New findings in adult opsoclonus-myoclonus syndrome. *JAMA Neurol* 2016; 73: 381-2.
81. Berger JR, Mehari E. Paraneoplastic opsoclonus-myoclonus secondary to malignant melanoma. *J Neurooncol* 1999; 41: 43-5.
82. Jung KY, Youn J, Chung CS. Opsoclonus-myoclonus syndrome in an adult with malignant melanoma. *J Neurol* 2006; 253: 942-3.
83. Vedeler CA, Antoine JC, Giometto B, et al. Paraneoplastic neurological syndromes. In: *European Handbook of Neurological Management*. Gilhus NE, Barnes MP, Brainin M, editors. Singapore: Blackwell Publishing Ltd; 2011; 447-57.
84. Joubert B, Rostásy K, Honnorat J. Immune-mediated ataxias. *Handb Clin Neurol* 2018; 155: 313-32.
85. Schiller M, Bohm M, Hensen P, et al. Dermatomyositis associated with malignant melanoma – a marker of poor prognosis? *J Am Acad Dermatol* 2006; 54: 221-6.