Review paper

# Paraneoplastic syndromes in patients with melanoma

**Michał Dec, Hubert Arasiewicz**

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

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## 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

**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
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**Table 1.** The study flowchart

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

of 392 papers, including abstracts, original texts, and case reports, were identified. A total of 270 publications were 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 statistically significant association exists between the malignancy and a specific cutaneous disease. and/or 5) A genetic as-

**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 dysdiadochokinesia | 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 | Simulta-neously | Surgery | Yes |
| 15 | Bilateral diffuse uveal melanocytic proliferation (B-DUMP) | F | 70 | N/A | No/No | Simulta-neously | 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 | Simulta-neously | 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 | Simulta-neously | 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 | Simulta-neously | Surgery | Yes |
| 53 | Subacute cutaneous lupus erythematosus (SCLE) | M | 52 | Abdomen | No/No | Simulta-neously | 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 | Simulta-neously | 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; simultaneous: PNS present at the time of tumour diagnosis; after: PNS diagnosis after tumour diagnosis.*

sociation 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 this protection for the patient [32]. Conducting larger

**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.*

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 [78, 79]. 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 [7, 78, 80]. 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 [81]. 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 [82]. 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 [43]. 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.

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## Ethical approval

Not applicable.

## Conflict of interest

The authors declare no conflict of interest.

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