


ORIGINAL RESEARCH

Clinical characteristics of paraneoplastic syndromes in patients with head and neck cancer

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Abstract

Background: To summarize the clinical manifestations, diagnosis, and prognosis of head and neck cancer (HNC) patients with paraneoplastic syndromes (PNS).

Methods: The clinical data of 1958 patients with HNC admitted to our hospital from January 1996 to December 2020 were retrospectively analyzed. Demographic and cancer-related characteristics were extracted. Kaplan–Meier survival curves were compared by log-rank test. Cox regression was performed to evaluate prognostic factors and hazard ratio.

Results: Totally 40 HNC patients with PNS were included in the final analysis, including 36 men and four women with a mean age of 60.4 years (range 40–82). PNS was dermatologic or cutaneous in 23 (57.50%) patients, endocrine in 10 (25.00%), neurologic in five (12.50%), and osteoarticular or rheumatologic in two (5.00%). Twenty-five (62.50%) patients had Stage III/IV cancer. PNS regressed after antitumor therapy in 28 (70.00%) patients. Recurrence of PNS was observed in nine of 12 (75.00%) patients with cancer recurrence or metastasis. The 5-year overall survival (OS) and disease-free survival (DFS) rates of patients with PNS were 51.52% and 44.44%, respectively. The DFS ($p = .001$) and OS ($p = .003$) of patients presented with PNS prior to HNC diagnosis were significantly longer than those of patients with synchronous or metachronous PNS. PNS diagnosed before HNC (adjusted hazard ratio [aHR]: 0.31, 95% confidence interval [CI]: 0.11–0.85, $p = .02$), Stage IV disease (aHR: 3.27, 95% CI: 1.18–9.05, $p = .02$), and smoking history (aHR: 3.69, 95% CI: 1.04–13.05, $p = .04$) were significantly associated with OS and DFS.

Conclusions: Early recognition of PNS could provide clues about underlying tumor condition and result in early diagnosis. Prompt detection of cancer-associated syndromes could lead to a more favorable prognosis for these patients.

KEYWORDS

head and neck cancer, paraneoplastic syndrome, prognosis, treatment

Wenwen Diao and Ya Liang contributed equally to this study.

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1 | BACKGROUND

Paraneoplastic syndrome (PNS) in patients with malignant tumors is defined as a series of clinical signs and symptoms that are caused by tumor-related biological factors, including hormones, antibodies, lymphocytes, and cytokines, rather than by direct tumor invasion or metastasis or disruption of normal functions of the involved organs or tissues.¹ PNS may occur prior to, concurrent with, or subsequent to an underlying malignancy.²

PNS, which is also called paraneoplastic conditions, paraneoplastic effects, paraneoplastic phenomena, paraneoplastic disturbances, and remote effects, was first reported in cancer patients in 1949.³ PNS has a wide range of clinical manifestations and can involve multiple organs. It has been classified into six types⁴: cutaneous or dermatologic, endocrine, neurologic, osteoarticular or rheumatologic, hematologic, and ocular. Endocrine PNS is widely distributed in the lungs, gastrointestinal tract, pancreas, thyroid gland, adrenal medulla, and skin.⁴ PNS rarely involves patients with head and neck cancer (HNC), but may be the first or most distinguishing manifestation. The most frequent type of PNS in patients with malignancies of the larynx and hypopharynx is dermatologic, particularly Bazex syndrome (acrokeratosis paraneoplastica)⁵ followed by hypercalcemia.

The appearance of PNS has been shown to be associated with a poor prognosis of patients, and influence the selection of treatment strategy. Identifying PNS is also clinically important, as it can be diagnostic of cancer at a relatively early stage, thus improving patient survival. Only a few case reports or studies with a small sample size have evaluated PNS in patients with HNC. Herein, this study aimed to explore the association between PNS and HNC.

2 | PATIENTS AND METHODS

2.1 | Patients

This retrospective study included patients diagnosed with HNC who were admitted to Peking Union Medical College Hospital from January 1996 to December 2020. In the process of diagnosis and treatment for patients with head and neck tumors diagnosed in hospital outpatient clinics, nasopharyngeal cancer, hypopharyngeal cancer, and laryngeal cancer are mainly treated by the Department of Otolaryngology-Head and Neck Surgery. Whereas, all patients with oral cavity cancer and some patients with oropharynx cancer would be referred to the Department of Oral and Maxillofacial Surgery for surgical treatment according to the scope of the departments and individual willingness. In addition, patients with oropharynx cancer rarely consulted at our hospital. Therefore, there were no oral cavity cancer patients and few oropharynx cancer patients included in this study in our department. During the data collection phase, age, gender, smoking history, alcohol use, timing of PNS, type of PNS, type of HNC, tumor stage, tumor grade, immunohistochemical markers, serum biomarkers, recurrence, and survival time were extracted. Follow-up

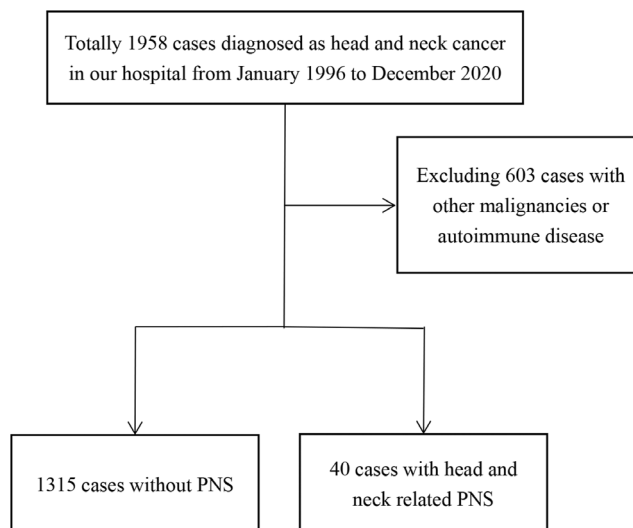


FIGURE 1 Flow chart of the analysis of patients with paraneoplastic syndromes

duration was calculated from the date of diagnosis. Follow-up information was based on outpatient medical records and telephone calls.

The study was approved by the Ethics Committee of Peking Union Medical College Hospital. Informed consent was not required of the patients given the retrospective nature of the study. Patient data were anonymized in the article.

Patients meeting these criteria were included: patients diagnosed with HNC. Patients with malignancies other than head and neck, or patients with autoimmune disease were excluded. The study flow-chart is shown in Figure 1.

2.2 | Diagnosis of PNS

PNS was diagnosed based on clinical, radiological, and/or biological manifestations associated with tumor without direct invasion. Of the six categories of PNS,⁴ four were observed in our study (cutaneous or dermatologic, endocrine, neurologic, osteoarticular, or rheumatologic). Each PNS type was diagnosed as previously described.⁶⁻⁹ These syndromes may occur before, at the same time, or after diagnosis of the underlying malignancy. Neoplasms and PNS may develop simultaneously, with treatment of the neoplasm resulting in regression of PNS and recurrence of the neoplasm being accompanied by recurrence of PNS in the absence of genetic or other possible causes.

2.3 | Statistical analysis

Overall survival (OS) was defined as the time from the date of treatment initiation to the date of death or last follow-up, and disease-free survival (DFS) was defined as the time from treatment initiation to the date of recurrence, death, or last follow-up. DFS was defined as the primary endpoint, whereas OS was the secondary endpoint.

TABLE 1 Demographic and cancer-related characteristics of patients included

	Site of primary tumor				Total	
	Larynx	Oropharynx	Hypopharynx	Nasopharynx		
Sex						
Male	20	2	4	10	36	90.00%
Female	2	0	0	2	4	10.00%
Age (year)						
≤55	6	0	1	3	10	25.00%
>55	16	2	3	9	30	75.00%
Smoking history						
Yes	15	1	3	8	27	67.50%
No	7	1	1	4	13	32.50%
Alcohol use						
Yes	9	0	4	5	18	45.00%
No	13	0	0	7	22	55.00%
PNS type						
Cutaneous	11	1	3	8	23	57.50%
Endocrine	7	0	0	3	10	25.00%
Neurologic	2	1	1	1	5	12.50%
Rheumatic	2	0	0	0	2	5.00%
Timing of PNS						
Prior	13	2	3	7	25	62.50%
Synchronous	3	0	0	1	4	10.00%
Metachronous	6	0	1	4	11	27.50%
TNM stage						
I	3	1	0	1	5	12.50%
II	6	0	1	3	10	25.00%
III	4	0	2	3	9	22.50%
IV	9	1	1	5	16	40.00%
Histology						
Squamous cell carcinoma	12	2	4	12	30	75.00%
Neuroendocrine neoplasms	4	0	0	0	4	10.00%
Adenocarcinoma	5	0	0	0	5	12.50%
Undifferentiated carcinoma	1	0	0	0	1	2.50%
Treatment						
S	6	0	0	0	6	15.00%
RT	2	1	0	1	4	10.00%
S + RT	9	0	2	0	11	27.50%
S + CRT	2	0	1	0	3	7.50%
CRT	3	1	1	11	16	40.00%

Abbreviations: CRT, chemoradiotherapy; PNS, paraneoplastic syndrome; RT, radiotherapy; S, surgery.

All the data collected in this study were analyzed using SPSS 22.0 software. Categorical data were expressed as *n* (%), and differences between the two groups were examined by chi-square test or Fisher's exact test. OS and DFS were calculated using Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox regression were performed to assess prognostic factors and corresponding hazard ratios. *p* Value <.05 was considered statistically significant.

3 | RESULTS

During the study period, 1958 patients (1588 men and 370 women) were diagnosed with HNC. Of these patients, 1258 (62.25%) were diagnosed with laryngeal carcinoma, 238 (12.16%) with hypopharyngeal carcinoma, 85 (4.34%) with oropharyngeal carcinoma, and 377 (19.25%) with nasopharyngeal carcinoma. There were 40 patients

(2.04% of all HNC), including 36 men (90.00% of PNS patients) and four women (10.00%) with a mean age of 60.4 years (range: 40–82 years), were diagnosed with PNS. Twenty-seven patients (67.50%) were current or former smokers, and 20 (50.00%) were drinkers. Squamous cell carcinoma was the most common pathological type, occurring in 30 patients (75.00%).

PNS was dermatologic or cutaneous in 23 (57.50%) patients, endocrine in 10 (25.00%), neurologic in five (12.50%), and osteoarticular or rheumatologic in two (5.00%). The diagnosis of PNS was synchronous (within 1 month after cancer diagnosis) in four (10.00%) patients, metachronous (longer than 1 month after cancer diagnosis) (mean 4 months, range 1–9 months) in 11 (27.50%), and preceding cancer diagnosis (mean 5.3 months, range 1–16 months) in 25 (62.50%). Twenty-five patients (62.50%) had Stage III/IV disease, five (12.50%) had Stage I, and 10 (25.00%) had Stage II tumor.

Patients with PNS diagnosed after HNC tended to have more advanced-stage tumors (Stage III–IV, 9/11). All demographic and cancer-related characteristics of these 40 patients are listed in Table 1.

Of 23 patients presented with paraneoplastic skin lesions, including 13 (56.52%) with Bazex syndrome, five (21.74%) with acanthosis nigricans, three (13.04%) with dermatomyositis, and two (8.70%) with bullous pemphigus. Besides, the onset of PNS tended to be more rapidly resistant to routine treatment. Of the 10 patients with endocrine PNS, six (60.00%) had hypercalcemia, three (30.00%) had syndrome of inappropriate antidiuretic hormone (SIADH) and one (10.00%) had ectopic adrenocorticotrophic hormone syndrome. Of the five patients with neurologic PNS, three (60.00%) had cerebellar degeneration, one (20.00%) had encephalomyelitis, and one (10.00%) had Lambert–Eaton syndrome. The electromyogram of the patient with

TABLE 2 Univariate and multivariate analysis of risk factors for OS and DFS among HNC patients with PNS

	DFS			OS		
	Univariate analysis (p)	Multivariate analysis		Univariate analysis (p)	Multivariate analysis	
		aHR (95% CI)	p		aHR (95% CI)	p
Sex						
Male	.39			.12		
Female						
Age (year)						
≤55	.41			.29		
>55						
Smoking history						
Yes	.08	3.13 (1.02–9.64)	.047	.05	3.69 (1.04–13.05)	.04
No						
Alcohol use						
Yes	.80			.87		
No						
Neoplasm site						
Larynx	.98			.96		
Other						
PNS type						
Cutaneous	.40			.13		
None-cutaneous						
Timing of PNS						
Prior	.001	0.33 (0.13–0.87)	.02	.003	0.31 (0.11–0.85)	.02
Syn–/metachronous						
TNM stage						
IV	< .001	4.74 (1.75–12.83)	.002	.007	3.27 (1.18–9.05)	.02
I/II/III						
Treatment						
S ± RT/CRT	.76			.93		
RT/CRT						

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; DFS, disease-free survival; OS, overall survival; PNS, paraneoplastic syndrome; RT, radiotherapy; S, surgery.

TABLE 3 Review of published series consisting of HNC patients with PNS cases

Year of publication	No. of patients	Sex, M/F	Median age	Type of HNC (number of patients)	Type of PNS	Treatment	Follow-up (median months)	Ref
2002	1	1/0	66	Hypopharyngeal Carcinoma	Polyarteritis	CRT + methylprednisolone	6	10
2003	2	2/0	58	Nasopharyngeal carcinoma (1) Oropharyngeal carcinomas (1)	Dermatomyositis (2)	CRT+ prednisone (2)	15.5	11
2006	4	3/1	66	Nasopharyngeal carcinoma (1) Nasopharyngeal lymphoma (1) Hypopharyngeal carcinoma (1) Laryngeal carcinoma (1)	Dermatological (1) Endocrine (1) Rheumatological (1) Encephalomyelitis (1)	RT (1)/CT (1)/ S + RT (1)/ IT (1)	3.5	12
2009	1	1/0	60	Oropharyngeal carcinoma	Bazex syndrome	S + RT	36	13
2009	1	1/0	46	Laryngeal carcinoma	Dermatological	S	12	14
2010	2	1/1	28	Nasopharyngeal carcinoma (2)	Hematologic syndromes (2)	CRT+ prednisone (2)	19	15
2011	1	1/0	58	Nasopharyngeal carcinoma	Dermatomyositis	S + CRT	60	16
2013	1	1/0	38	Oropharyngeal lymphoepithelial carcinoma	Cerebellar degeneration	S+ prednisone	18	17
2014	1	1/0	63	Oropharyngeal carcinoma	Dermatomyositis	S + CRT	11	18
2015	1	1/0	52	Hypopharyngeal carcinoma	Hematologic syndromes	Palliative RT	3	19
2015	1	1/0	60	Hypopharyngeal carcinoma	rheumatological	CRT	5	20
2017	1	1/0	68	Oropharyngeal carcinoma	Neurological syndrome	CRT	18	21
2018	1	1/0	78	Oropharyngeal neuroendocrine carcinoma	Lambert–Eaton myasthenic syndrome	CRT	16	22
2019	1	1/0	Middle-aged	Nasopharyngeal carcinoma	Cerebellar Degeneration	CRT	NR	23
2021	1	1/0	68	Laryngeal neuroendocrine carcinoma	Lambert–Eaton myasthenic	S+ CRT	36	24
2021	10	5/5	50	Nasopharyngeal carcinoma (10)	Dermatomyositis (10)	RT (3)/CRT (6)/Palliative CRT (1)	15/NR (1)	25

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; F, female; HNC, head and neck cancer; IT, immunotherapy; M, male; NR, no report; PNS, paraneoplastic syndrome; Ref, reference number; RT, radiotherapy; S, surgery.

Lambert–Eaton syndrome showed facilitation after high frequency continuous electrical stimulation. Anti-Hu and anti-Yo antibodies were detected in the serum and the cerebrospinal fluid of two patients with cerebellar degeneration, with no specific antibody detected in the other three patients with neurologic PNS. Patients with paraneoplastic arthritis complained of acute asymmetric polyarthritis but had no specific biological or radiological features. No patient was diagnosed with rheumatoid nodules or was positive for rheumatoid factor or antinuclear antibodies.

For treatment strategy, 20 patients underwent surgery with or without radiotherapy and chemoradiotherapy, four patients with early stage disease received radiotherapy alone, and the remaining 16 patients, including 11 with nasopharyngeal carcinoma, were administered with chemotherapy. As to survival status, 17 patients died before the last follow-up. One patient with laryngeal small cell endocrine carcinoma and hypercalcemia died of the disease before completion of anticancer treatment, and one patient with atypical

carcinoid and encephalomyelitis died of tumor after surgery. Five of the 16 patients who received chemoradiotherapy without complete response died at 14, 18, 28, 40, and 51 months, respectively. Ten patients died 8–76 months (median 26 months) after cancer recurrence or metastasis after complete remission.

Symptomatic treatments for PNS included skin-directed therapy for cutaneous PNS, intravenous fluids/bisphosphonates for hypercalcemia, ketoconazole/metyrapone for Cushing's syndrome (CS), fluid restriction for SIADH, immunomodulatory therapy for neurologic PNS and NSAIDs, and steroids for rheumatologic PNS. Of all these 40 patients, 31 (77.50%) received local and systemic treatment (including surgery, radiotherapy, surgery plus radiotherapy, surgery plus chemoradiotherapy, and chemoradiotherapy). PNS regressed after treatment of tumor. Nine of the 12 patients who experienced cancer recurrence or metastasis also had recurrence of PNS.

The median follow-up time was 40.5 months (range: 2–269 months). The 5-year OS and DFS rates for HNC patients with PNS were 51.52% and 44.44%, respectively. The OS and DFS rates were significantly different among patients with different types of PNS. The DFS ($p = .001$) and OS ($p = .003$) of patients who presented with PNS prior to HNC diagnosis were significantly longer than those of patients with synchronous or metachronous PNS. Stage IV disease was associated with significantly poorer DFS ($p < .001$) and OS ($p = .007$) compared with other stages. There was a trend of shorter DFS ($p = .08$) and OS ($p = .05$) in patients with a history of smoking compared with those without, but there was no statistical difference.

Table 2 shows the prognostic factors of OS and DFS based on Cox regression analysis. PNS diagnosed before HNC (adjusted hazard ratio [aHR]: 0.31, 95% CI: 0.11–0.85, $p = .02$), Stage IV disease (aHR: 3.27, 95% CI: 1.18–9.05, $p = .02$) and smoking history (aHR: 3.69, 95%CI: 1.04–13.05, $p = .04$) were significantly associated with OS and DFS.

Our literature review included 30 HNC patients with PNS (9, 40–54). The clinical characteristics, treatments, and outcomes of these patients are summarized in Table 3. On PubMed, we searched 16 relevant full texts with paraneoplastic syndromes and head and neck cancer as the subject words over the recent 20 years. Male patients accounted for a greater proportion of patients in these studies (27/30). The median age of the patients was 60 years in these studies. Squamous cell carcinoma (16/30) was the mainly histological type. The majority of the PNS cases were cutaneous (17/30). All characteristics mentioned above in these studies are consistent with ours. However, more than half of the primary tumor sites were nasopharynx (17/30). Among these studies, systemic treatment was the most common. Most paraneoplastic skin lesions responded well to glucocorticoid. Eight cases with available follow-up data died of primary tumor and the other cases were alive during the follow-up period.

4 | DISCUSSION

PNS develops during different phases of the cancer process, with an estimated incidence of 1%–8%.^{5,12,26} The appearance of PNS may be

the first sign of malignancy in a few cancer patients facilitating diagnosis at early and potentially reversible stage.²⁷ However, PNS associated with HNC is rare, and the incidence of PNS in patients with HNC remains unclear. To the best of our knowledge, this is the first study enrolling the largest sample size of HNC patients with PNS.

Paraneoplastic cutaneous and dermatologic syndromes, consisting of many cutaneous lesions,²⁸ were the most common type of PNS in HNC patients in the present study. Four types of paraneoplastic skin lesions were observed in 23 patients. Bazex syndrome has been reported to be the most frequent paraneoplastic lesion of the skin. These lesions are commonly atypically located, with blue to violet discoloration, and are refractory to treatment.²⁹ Acanthosis nigricans is often associated with abdominal adenocarcinoma, with 60% of them arising in the stomach. However, acanthosis nigricans is also associated with larynx³⁰ and hypopharynx squamous cell carcinoma.³¹ Bullous pemphigoid is a fairly common subepidermal blistering disease and is associated with many tumor types, including carcinoma of the larynx.³² Of the 23 patients with paraneoplastic cutaneous and dermatologic syndromes, 16 were diagnosed with PNS before HNC, and their prognosis was significantly better than that of patients with other types of PNS.

Most endocrine PNS associated with non-endocrine neoplasms were observed in patients with highly malignant tumors, such as lung, breast, prostate, ovarian, skin, colon cancers, and hematological malignancies.⁶ However, endocrine PNS may be associated with tumors arising from various tissue actually.^{33–38} Hypercalcemia of malignancy is one of the most common types of endocrine PNS, with an incidence up to 10% among advanced-stage tumors, and a nearly 50% 30-day mortality rate.^{39,40} Eighty percent of hypercalcemic patients with solid tumors had increased concentrations of parathyroid hormone-related protein in plasma.⁴¹ The mean survival time after the diagnosis of hypercalcemia in cancer patients is about 54.9 days, making hypercalcemia an important negative prognostic factor for them.⁴² Calcium concentrations should be measured regularly for cancer patients with poor status irrespective of tumor stage.⁴³ In the present study, six patients diagnosed with hypercalcemia all had advanced disease, and four of them died at 4, 8, 15, and 18 months, respectively.

SIADH is observed in 1%–2% of patients with malignant tumors.^{38,44} Hyponatremia is associated with increased all-cause mortality and increased risk of malignancies, especially lung and head-and-neck.⁴⁵ Successful treatment of the underlying tumor resulted in the normalization of sodium concentration within several weeks. CS is considered to be of paraneoplastic origin in approximately 10% of the patients diagnosed with this disease, and approximately half of them have CS secondary to lung neuroendocrine tumors.^{46–48} CS in these patients is caused by tumor secretion of adrenocorticotrophic hormone or corticotrophin-releasing hormone.^{49,50} Neither SIADH nor CS is common in patients with HNC. In our study, three patients had SIADH, and two of them died at 40 and 41 months, respectively. The remaining one patient was alive without disease at 150 months. CS was observed in only one patient with laryngeal small cell neuroendocrine carcinoma, who was alive with no evidence of disease 201 months after surgery and radiotherapy. None of these patients was observed to have carcinoid syndrome.

PNS is regarded as autoimmune condition due to the activation of the immune system destroying distant tumors. It occurs frequently in cancer patients, but has been reported occasionally in patients with laryngeal cancers. Because neural tissues secrete onconeural proteins, they are damaged by immune-mediated inflammation.⁴⁴ Both central and peripheral nervous systems could be affected. The median survival of patients with positive anti-Hu antibodies is significantly longer than that of negative ones, regardless of the primary tumor stage.⁵¹ The detection of paraneoplastic antineuronal autoantibodies could lead to the diagnosis of the underlying primary malignancy or recurrent tumor.^{52,53} The present study included three patients with cerebellar degenerations, of whom two were found to have anti-Hu and anti-Yo antibodies in serum and cerebrospinal fluid^{53,54} and were alive at 14 and 74 months, respectively.

The key features of paraneoplastic rheumatism included a short interval between arthritis and neoplasia (within 12 months before or after cancer diagnosis), older age, asymmetric joint involvement, sudden onset, greater predominance in the lower extremities than in hands and wrists, absence of rheumatoid factor, rheumatoid nodules and erosions on radiograph, no family history of rheumatic disease, and nonspecific synovial histopathology.⁵⁵ All of these features were present in our patients without symmetry and hand involvement, which has been reported previously.⁵⁶ Tumors in two patients were diagnosed after articular PNS had laryngeal squamous cell carcinoma. One of them died of lung metastasis at 76 months after surgery and postoperative radiotherapy, and the other was alive 34 months after surgery.

Treatment approaches for these patients depended on the type and location of PNS. Neurologic PNS, such as paraneoplastic limbic encephalitis, subacute sensory neuronopathy, and paraneoplastic cerebellar degeneration, required immediate symptomatic treatment to prevent devastating neurologic disability or death. Treatment strategies are composed of two aspects: treatment of the underlying tumor, consisting of combinations of surgery and radiation/chemotherapy generally applied to these neoplastic disorders in the absence of PNS and treatment of the presumptive immune-mediated disorder, based on immunosuppression with intravenous immunoglobulins, steroids, other immunosuppressive drugs or plasma exchange.⁵⁷ However, immune therapy usually has no or modest effect on the central nervous system syndromes, whereas such therapy is beneficial for PNS affecting the neuromuscular junction. Symptomatic therapy should be offered to all patients with PNS.¹⁰

Because dermatological PNS frequently precedes the underlying tumor, timely recognition of PNS may improve the prognosis of patients. However, hypercalcemia is often a late manifestation of the tumor and has a negative prognostic impact. PNS type was not a significant predictor of patient outcomes, which might be due to the small number of patients in each group. In the present study, the median follow-up time was 41.5 months, with a 5-year OS and DFS rate of 57% and 53%, respectively. Factors significantly associated with OS and DFS included PNS diagnosed before HNC, Stage IV disease, and smoking history.

There were also several limitations in this study. First, there were unavoidable biases due to its retrospective nature. Second, this was a single-center analysis with a limited number of patients, unless it enrolled much more patients than any other studies published before. In addition, as described in the methods, there were no oral cavity cancer patients and few oropharynx cancer patients included in this study in our department, which might induce an unavoidable selection bias, and future cohort study that include oral cavity cancer and other sites of head and neck cancers is need to further explore the prevalence and manifestations of PNS. Thus, all conclusions should be interpreted with caution.

5 | CONCLUSIONS

In conclusion, a prompt and correct diagnosis of any type of PNS could lead to better prognosis. Early recognition of PNS may provide clues about underlying tumor condition and result in early diagnosis. Timely detection of cancer-associated syndromes could give more favorable prognosis for these patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used during this study are available from the corresponding author on reasonable request.

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REFERENCES

1. Ferlito A, Elsheikh MN, Manni JJ, Rinaldo A. Paraneoplastic syndromes in patients with primary head and neck cancer. *Eur Arch Otorhinolaryngol*. 2007;264(3):211-222.
2. Ferlito A, Rinaldo A, Devaney KO. Syndrome of inappropriate antidiuretic hormone secretion associated with head and neck cancers: review of the literature. *Ann Otol Rhinol Laryngol*. 1997;106:878-883.
3. Guichard A, Dignon G. La polyradiculoneurite cancéreuse métastatique. *JMed Lyon*. 1949;30:197-207.
4. Ferlito A, Rinaldo A. Paraneoplastic syndromes in patients with cancer of the larynx and hypopharynx. *Ann Otol Rhinol Laryngol*. 2007;116(7):502-513.
5. Ferlito A, Rinaldo A. Paraneoplastic syndromes in patients with laryngeal and hypopharyngeal cancers. *Ann Otol Rhinol Laryngol*. 2000;109(1):109-117.
6. Dimitriadis GK, Angelousi A, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Paraneoplastic endocrine syndromes. *Endocr Relat Cancer*. 2017;24(6):R173-R190.
7. Silva JA, Mesquita Kde C, Igreja AC, et al. Paraneoplastic cutaneous manifestations: concepts and updates. *An Bras Dermatol*. 2013;88(1):9-22.

8. Graus F, Delattre J, Antoine J, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1135-1140.
9. Morel J, Deschamps V, Toussiroit E, et al. Characteristics and survival of 26 patients with paraneoplastic arthritis. *Ann Rheum Dis*. 2008;67(2):244-247.
10. Vedeler CA, Antoine JC, Giometto B, et al. Management of paraneoplastic neurological syndromes: report of an EFNS task force. *Eur J Neurol*. 2006;13(7):682-690.
11. Botsios C, Ostuni P, Boscolo-Rizzo P, Da Mosto MC, Punzi L, Marchiori C. Dermatomyositis and malignancy of the pharynx in Caucasian patients: report of two observations. *Rheumatol Int*. 2003;23(6):309-311. doi:10.1007/s00296-003-0319-y
12. Baijens LW, Manni JJ. Paraneoplastic syndromes in patients with primary malignancies of the head and neck. Four cases and a review of the literature. *Eur Arch Otorhinolaryngol*. 2006;263(1):32-36.
13. Fasanmade A, Farrell K, Perkins CS. Bazex syndrome (acrokeratosis paraneoplastica): persistence of cutaneous lesions after successful treatment of an associated oropharyngeal neoplasm. *Br J Oral Maxillofac Surg*. 2009;47(2):138-139. doi:10.1016/j.bjoms.2008.07.190
14. Batinac T, Kujundžić M, Peternel S, Cabrijan L, Troselj-Vukić B, Petranović D. Pityriasis rubra pilaris in association with laryngeal carcinoma. *Clin Exp Dermatol*. 2009;34(8):e917-e919. doi:10.1111/j.1365-2230.2009.03701.x
15. Yang K, Zhang T, Chen J, et al. Immune thrombocytopenia as a paraneoplastic syndrome in patients with nasopharyngeal cancer. *Head Neck*. 2012;34(1):127-130. doi:10.1002/hed.21481
16. Chakroun A, Guigay J, Lusinchi A, Marandas P, Janot F, Hartl DM. Paraneoplastic dermatomyositis accompanying nasopharyngeal carcinoma: diagnosis, treatment and prognosis. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2011;128(3):127-131. doi:10.1016/j.anorl.2010.10.007
17. Henke C, Rieger J, Hartmann S, Middendorp M, Steinmetz H, Ziemann U. Paraneoplastic cerebellar degeneration associated with lymphoepithelial carcinoma of the tonsil. *BMC Neurol*. 2013;17(13):147. doi:10.1186/1471-2377-13-147
18. Adi AH, Alturkmani H, Spock T, et al. Dermatomyositis paraneoplastic syndrome before symptomatic tonsillar squamous cell carcinoma: a case report. *Head Neck*. 2014;37(1):E1-E3. doi:10.1002/hed.23703
19. Subramaniam N, Hiremath B. Leukemoid reaction as a paraneoplastic syndrome in hypopharyngeal squamous cell carcinoma with cutaneous metastasis: an exceedingly rare occurrence. *BMJ Case Rep*. 2015;2015:bcr2015211007. doi:10.1136/bcr-2015-211007
20. Yang L, Li W, Du J. Piriform sinus carcinoma with a paraneoplastic syndrome misdiagnosed as adult onset Still's disease: a case report. *Int J Clin Exp Med*. 2015;8(10):19581-19585.
21. Yong L, Asimakopoulos P, Mumford C, Fragkandrea NI. When dizziness becomes sinister: oropharyngeal carcinoma presenting as a paraneoplastic neurological disorder. *BMJ Case Rep*. 2017;2017:bcr2016216151. doi:10.1136/bcr-2016-216151
22. Takasugi J, Shimamura M, Koda T, et al. Paraneoplastic cerebellar degeneration and Lambert-Eaton myasthenic syndrome associated with neuroendocrine carcinoma of the oropharynx. *Intern Med*. 2018;57(4):587-590. doi:10.2169/internalmedicine.9333-17
23. Bhardwaj S, Khasani S, Benasher D, et al. Paraneoplastic cerebellar degeneration in nasopharyngeal carcinoma: a unique association. *The Cerebellum*. 2019;18(6):1126-1129. doi:10.1007/s12311-019-01045-1
24. Mesolella M, Allosso S, Buono S, Ricciardiello F, Motta G. Neuroendocrine carcinoma of the larynx with Lambert-Eaton myasthenic syndrome: a rare case report and literature review. *J Int Med Res*. 2021;49(5):3000605211014784. doi:10.1177/03000605211014784
25. Lau L, Huang L, Fu E, Tan TC, Kong KO, Lim MY. Nasopharyngeal carcinoma in dermatomyositis. *Clinical Otolaryngol*. 2021;46(5):1082-1088. doi:10.1016/j.rpor.2014.02.005
26. Gulya AJ. Neurologic paraneoplastic syndromes with neurotologic manifestations. *Laryngoscope*. 1993;103(7):754-761.
27. Tarin D. Update on clinical and mechanistic aspects of paraneoplastic syndromes. *Cancer Metastasis Rev*. 2013;32(3-4):707-721.
28. Kurzrock R, Cohen PR. Cutaneous paraneoplastic syndromes in solid tumors. *Am J Med*. 1995;99(6):662-671.
29. Räßler F, Goetze S, Elsner P. Acrokeratosis paraneoplastica (Bazex syndrome) - a systematic review on risk factors, diagnosis, prognosis and management. *J Eur Acad Dermatol Venereol*. 2017;31(7):1119-1136. doi:10.1111/jdv.14199
30. Oppolzer G, Schwarz T, Zechner G, Gschnait F. Acanthosis nigricans in squamous cell carcinoma of the larynx. *Z Hautkr*. 1986;61(17):1229-1237.
31. Miller TR, Davis J. Acanthosis nigricans occurring in association with squamous carcinoma of the hypopharynx. *N Y State J Med*. 1954;54(16):2333-2336.
32. Hodge L, Marsden RA, Black MM, Bhogal B, Corbett MF. Bullous pemphigoid: the frequency of mucosal involvement and concurrent malignancy related to indirect immunofluorescence findings. *Br J Dermatol*. 1981;105(1):65-69.
33. Lorch G, Gilmore JL, Koltz PF, et al. Inhibition of epidermal growth factor receptor signalling reduces hypercalcaemia induced by human lung squamous-cell carcinoma in athymic mice. *Br J Cancer*. 2007;97(2):183-193.
34. Nimalasena S, Freeman A, Harland S. Paraneoplastic Cushing's syndrome in prostate cancer: a difficult management problem. *BJU Int*. 2008;101(4):424-427.
35. Gilmore JL, Gonterman RM, Menon K, et al. Reconstitution of amphiregulin-epidermal growth factor receptor signaling in lung squamous cell carcinomas activates PTHrP gene expression and contributes to cancer-mediated diseases of the bone. *Mol Cancer Res*. 2009;7(10):1714-1728.
36. Nella A, Lodish M, Fox E, et al. Vandetanib successfully controls medullary thyroid cancer-related Cushing syndrome in an adolescent patient. *J Clin Endocrinol Metabol*. 2014;99(9):3055-3059.
37. Dimitriadis G, Gopalakrishnan K, Rao R, et al. Severe paraneoplastic hypoglycemia secondary to a gastrointestinal stromal tumour masquerading as a stroke. *Endocrinol Diabetes Metab Case Rep*. 2015;2015(1):150062.
38. Thajudeen B, Salahudeen AK. Role of tolvaptan in the management of hyponatremia in patients with lung and other cancers: current data and future perspectives. *Cancer Manage Res*. 2016;8:105-114.
39. Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer-associated hypercalcaemia: morbidity and mortality. *Ann Intern Med*. 1990;112(7):499-504.
40. Lumachi F, Brunello A, Roma A, Basso U. Medical treatment of malignancy-associated hypercalcaemia. *Curr Med Chem*. 2008;15(4):415-421.
41. Clines G, Guise T. Hypercalcaemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis to bone. *Endocr Relat Cancer*. 2005;12(3):549-583.
42. Sridhar KS, Hussein AM. Hypercalcaemia in head and neck squamous-cell carcinoma. *Am J Clin Oncol*. 1990;13(5):388-393.
43. Bradley PJ, Hoskin D. Hypercalcaemia in head and neck squamous cell carcinoma. *Curr Opin Otolaryngol Head Neck Surg*. 2006;14(2):51-54.
44. Voltz R. Paraneoplastic neurological syndromes: an update on diagnosis, pathogenesis, and therapy. *Lancet Neurol*. 2002;1(5):294-305.
45. Selmer C, Madsen JC, Torp-Pedersen C, Gislason GH, Faber J. Hyponatremia, all-cause mortality, and risk of cancer diagnoses in the primary care setting: a large population study. *Eur J Intern Med*. 2016;36:36-43.
46. Barbosa SL, Rodien P, Lebouleux S, et al. Ectopic adrenocorticotrophic hormone-syndrome in medullary carcinoma of the thyroid: a retrospective analysis and review of the literature. *Thyroid*. 2005;15(6):618-623.

47. Teves DA. Clinical approach of Cushing syndrome resulting from ACTH-producing metastatic neuroendocrine tumor. *Endocrinologist*. 2005;15(6):401-404.
48. Morandi U, Casali C, Rossi G. Bronchial typical carcinoid tumors. *Semin Thorac Cardiovasc Surg*. 2006;18(3):191-198.
49. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev*. 1998;19(5):647-672.
50. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet*. 2006;367(9522):1605-1617.
51. Graus F, Dalmou J, Rene R, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. *J Clin Oncol*. 1997;15(8):2866-2872.
52. Dalmau JO, Posner JB. Paraneoplastic syndromes. *Arch Neurol*. 1999; 56(4):405-408.
53. Mason WP, Graus F, Lang B, et al. Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert-Eaton myasthenic syndrome. *Brain*. 1997;120(Pt 8):1279-1300.
54. Baloh RW. Paraneoplastic cerebellar disorders. *Otolaryngol Head Neck Surg*. 1995;112(1):125-127.
55. Caldwell DS, McCallum RM. Rheumatologic manifestations of cancer. *Med Clin North Am*. 1986;70(2):385-417.
56. Zupancic M, Annamalai A, Brenneman J, Ranatunga S. Migratory polyarthritis as a paraneoplastic syndrome. *J Gen Intern Med*. 2008; 23(12):2136-2139.
57. Bologna JL, Brewer YP, Cooper DL. Bazex syndrome (acrokeratosis paraneoplastica). *Anal Rev Med*. 1991;70(4):269-280.

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