Retrospective Study

Analysis of Risk Factors for Postherpetic Neuralgia in Patients With Postmalignancy Herpes Zoster

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Background: The high risk of developing postherpetic neuralgia (PHN) is associated with severe immunosuppressive diseases. A malignancy itself, as well as surgery, radiotherapy, and other treatments, can lead to changes in the immune status of the body and predispose patients with a malignancy to PHN.

Objective: To investigate the risk factors of postherpetic neuralgia in herpes zoster (HZ) after a malignant tumor and to provide better preventive strategies for clinical practice.

Study Design: A retrospective cohort study.

Setting: The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China.

Methods: Patients who developed HZ after being diagnosed with a malignant tumor in the Affiliated Hospital of Southwest Medical University from September 2018 through March 2022 were included in the research. A total of 70 patients were included, including 31 men and 39 women, aged 18- 82 years old (mean, SD: 59.77 ± 13.95). According to the occurrence of PHN, they were divided into a non-PHN (n = 46) and a PHN group (n = 24). General information about the patients was collected, including clinical data, treatment status, and prognosis. Univariate and multivariate analyses were conducted of influencing factors.

Results: A total of 19 factors, including gender, age, and white blood cell count, were included. A univariate analysis showed that there were differences in age, tumor stage, Numeric Rating Scale (NRS-11) score, and the use of antiviral drugs between the 2 groups; these differences were statistically significant, $P<0.05$. A multifactorial analysis revealed that the acute phase NRS-11 score (odds ratio [OR] = 4.21; 95% CI, 1.59-2.24, $P = 0.004$), antiviral drug use (OR = 0.28; 95% CI, 0.10-0.82, $P = 0.020$), and tumor stage (OR = 0.28, 95% CI, 0.08-0.98, $P = 0.047$) were statistically significant for the effect of PHN occurring in postmalignancy HZ. There was a statistically significant difference between the group with severe pain in the acute phase NRS-11 score and the group with mild and moderate pain, $P < 0.05$. There was a statistically significant difference between the group treated with 2 antivirals and the group not treated with antivirals, $P < 0.05$.

Limitations: There are some limitations in our research. It was conducted at a single center, with a single race, and had a small sample size. A larger-scale study should be conducted to analyze the influencing factors of PHN in patients with herpes zoster after a malignant tumor.

Conclusion: The NRS-11 score in the acute phase, whether the use of antiviral drugs in sufficient quantities, and tumor staging are the influencing factors of PHN after malignant tumors.

Key words: Malignancy, herpes zoster, postherpetic neuralgia, antiviral, risk factors

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Herpes zoster (HZ) is a neurocutaneous inflammatory reaction caused by the reactivation of the varicella zoster virus (VZV) latent in sensory ganglia, characterized by clusters of cutaneous herpes and neuralgia distributed along the corresponding segments of sensory nerves (1). Postherpetic neuralgia (PHN) is defined as pain that persists for more than 3 months and beyond after the acute phase (2).

Habel et al (3) investigated 14,670 patients with malignant neoplasms and found that patients with malignant neoplasms were at greatly increased risk of HZ and that HZ-associated pain was common. The prevalence of HZ was 4.8 times higher in patients with malignant hematological diseases and 1.9 times higher in patients with solid tumors than in the general population. Forbes et al (4) also found an increased risk of PHN in patients with severe immunosuppressive diseases, such as leukemia. Much of the current research on risk factors for developing PHN has focused on patients with herpes simplex (5), diabetes (6) combined with herpes zoster, and other diseases. In contrast, there is a lack of research on the factors influencing the occurrence of PHN in patients with a malignancy post-HZ. To investigate the factors influencing the development of PHN in patients with HZ after a malignancy, we aimed to provide better prevention strategies for the clinic. We enrolled patients with a malignant neoplasm who presented with HZ afterwards from September 2018 through March 2022 in our hospital as the study population. Their general condition and the factors influencing the occurrence of PHN were analyzed.

Methods

Study Design and Ethics

This retrospective cohort study was clinically and ethically registered in the University Medical Research Filing Registry and approved by the Clinical Trials Ethics Committee of Southwest Medical University Hospital (No. KY2022349). We strictly adhered to the relevant requirements of the Declaration of Helsinki of the World Medical Association. The trial report complies with the Consolidated Standards of Reporting Trials (CONSORT) checklist.

Patients

Patients diagnosed with a malignancy and presenting with HZ after the diagnosis from September 2018 through March 2022 in our hospital were retrospectively analyzed as study patients. A total of 81 patients were included. After applying our inclusion and exclusion criteria, there were 74 patients. Four patients were lost to follow-up; 70 patients were finally included in the study. Among them, 31 were men and 39 were women. Their ages ranged from 18 to 82 years (mean, SD; 59.77 ± 13.95). There were 46 patients in the non-PHN group and 24 patients in the PHN group. Group determination was based on whether PHN occurred or not.

Inclusion criteria were: 1) all patients were pathologically diagnosed with a malignancy; 2) HZ occurred after the diagnosis of a malignancy; 3) PHN diagnostic criteria refers to those with pain lasting for more than 3 months or more after the acute phase (2); 4) chronic disease—those who had been diagnosed by a specialist and had been ill for more than 6 months.

Exclusion criteria were: 1) those lost to follow-up; 2) those whose benign tumors were benign; 3) those with mental disorders or unclear speech.

Outcome Assessments and Data Collection

All indicators were collected through the hospital electronic case system, including hospitalization time, disease duration, gender, age, tumor type, tumor stage, chemotherapy history, radiotherapy history, surgery history, biotherapy history, targeted therapy history, smoking history, alcohol history, diabetes mellitus, hypertension, coronary heart disease, Numeric Rating Scale (NRS-11) score, white blood cell count, lymphocyte count, lymphocyte rate, distribution of affected nerve segments, mode of antiviral therapy, presence of PHN, and survival at follow-up.

The NRS-11 is composed of 11 numbers from 0 to 10. Patients use these 11 numbers to describe the intensity of pain: the higher the number the more severe the pain level. Zero is no pain, one to 3 is mild pain, 4 to 6 is moderate pain, 7 to 9 is severe pain, and 10 is the worst possible pain.

The follow-up period ended on June 1, 2022. Follow-up data collected included the patient's quality of life situation, treatment outcome, and prognosis.

Statistical Analysis

The data were analyzed by SPSS 26.0 statistical software (IBM Corporation). Measurement data such as age, white blood cell count, etc. are in accordance with a normal distribution, and the mean is expressed in . Independent sample t test and the χ^2 test were used for comparison between groups. Counting data such as gender, tumor stage, etc. are expressed by the number of patients and percentage (%), and nonparametric tests and χ^2 tests were used. A logistic regression analy-

sis was used in a multivariate analysis, and the difference was statistically significant ($P < 0.05$).

Results

Univariate Analysis of the Occurrence of PHN in HZ Postmalignancy

There were 70 cases of herpes zoster occurring postmalignancy: 31 were men and 39 were women, 46 were in the non-PHN group and 24 were in the PHN group. Nineteen factors, such as gender, age, and white blood cell count, were included. The general data of the patients in the 2 groups were compared, as shown in Table 1.

Multifactorial Analysis of Factors Influencing the Occurrence of PHN in HZ After a Malignant Tumor

The occurrence of PHN in patients with postmalignancy HZ was taken as the dependent variable, and age, tumor stage, acute stage NRS-11 score, and antiviral drugs—which were statistically significant in

Table 1. *Univariate analysis of the influencing factors of herpes zoster after a malignant tumor.*

		Number	Non-PHN group	PHN group	χ^2 value	*P* value
Gender (men/women)	men	31	19	12	0.483	0.487
	women	39	27	12		
Age (years)	< 60 years	32	25	7	4.030	0.045
	≥ 60 years	38	21	17		
Leukocyte count	≤ 4.4 × 10^9/L	27	21	6	4.989	0.083
	4.4~11.9 × 10^9/L	39	24	14		
	≥11.9 × 10^9/L	4	1	3		
Lymphocyte count	≤1.8 × 10^9/L	54	38	16	2.728	0.256
	1.8~6.3 × 10^9/L	13	71	6		
	≥ 6.3 × 10^9/L	3	1	2		
Lymphocyte rate	≤ 23	37	23	14	2.376	0.305
	23~69	30	22	8		
	≥ 69	3	1	2		
Solid tumors	Yes	47	27	14	0.001	0.977
	No	29	19	10		
Tumor TNM Staging	Stage I	2	0	2	9.340	0.025
	Stage II	4	1	3		
	Stage III	51	38	13		
	Stage IV	13	7	6		
Chemotherapy	Yes	47	33	14	1.285	0.257
	No	23	13	10		
Radiation Therapy	Yes	13	8	5	0.124	0.725
	No	57	38	19		
Surgical treatment	Yes	22	16	6	0.700	0.403
	No	48	30	18		
Targeted Therapy	Yes	10	6	4	0.169	0.681
	No	60	40	20		
hypertension	Yes	10	5	5	1.279	0.258
	No	60	49	19		
Diabetes	Yes	11	5	6	2.378	0.124
	No	59	41	18		

Table 1 cont. *Univariate analysis of the influencing factors of herpes zoster after a malignant tumor.*

		Number	Non-PHN group	PHN group	χ^2 value	*P* value
Coronary heart disease	Yes	1	0	1	1.944	0.163
	No	69	46	23		
Smoking history	Yes	13	7	6	0.998	0.318
	No	57	39	18		
Drinking history	Yes	7	4	3	0.254	0.615
	No	63	42	21		
Distribution of nerve involvement	Trigeminal Nerve	6	5	1	2.807	0.591
	Cervical nerve	15	8	7		
	Thoracic nerve	34	22	12		
	Lumbar nerve	13	10	3		
	Sacral nerve	2	1	1		
Acute phase NRS-11 Score	≤ 3 points (mild)	16	13	3	9.885	0.007
	4~6points (moderate)	35	26	9		
	≥ 7 points (severe)ab	19	7	12		
Antiviral drugs	No antiviral use	6	2	4	6.101	0.047
	Single antiviral	31	18	13		
	Two-combination antiviralc	33	26	7		

Note: [a]$P < 0.05$, the severe pain group compared with the mild pain group; [b]$P < 0.05$, the severe pain group compared with the moderate pain group; [c]$P < 0.05$, Comparison of the 2-combination antiviral group with the group not using antivirals.

the univariate analysis—were taken as independent variables. Chemotherapy, radiotherapy, and surgery, although not statistically significant, are all important methods in current tumor treatment. They were included in the independent variables of the multifactorial logistic analysis, and the results were statistically significant according to $P < 0.05$. The results of logistic regression analysis with independent variables assignment were displayed in Table 2. It could be found that the acute phase NRS-11 score and antiviral drug use were the influential factors for the occurrence of PHN in patients with HZ after the development of a malignancy (Table 3).

Discussion

The occurrence of HZ after a malignant tumor or tumors is related to the condition of the patient's immune system. Treating malignant tumors with surgery, chemotherapeutic drugs, radiation therapy, and other antitumor treatments can cause changes in the body's immune system and increase the risk of developing HZ. However, there is a lack of studies on whether these factors affect its development into PHN.

Kramer et al (5) suggested that strong emotional pain perception and a decreased quality of life and physical function during the acute phase may be risk factors for the development of HZ into PHN. In our study, the study population selected was patients who developed HZ after a malignancy. A univariate analysis of the factors influencing the development of PHN showed that age (≥ 60 years old), the tumor's stage, the acute phase NRS-11 score, and antiviral use as influencing factors. A multivariate logistic regression analysis showed that the acute phase NRS-11 score, antiviral drugs, and the tumor's stage were the influencing factors.

The acute phase NRS-11 score was found to be one of the risk factors affecting the occurrence of PHN in patients with postmalignancy HZ, with a statistically significant difference ($P < 0.05$) between the incidence of PHN in the severe pain group 63.2% (12/19) compared with 25.7% (9/35) in the mild pain group, and 18.8% (3/16) in the moderate pain group. That is, the more severe the pain level, the more likely PHN occurs.

A possible reason why pain level is an influential factor in the occurrence of PHN is that acute phase pain is caused by the activation of the latent VZV, with massive replication and rapid multiplication, causing nerve fiber necrosis to occur as a neuroimmune response (7). Steain, et al (8) studied the process of VZV activation in human ganglia, showing an immune response in

ganglia and nerve fibers. The affected ganglia showed necrosis and hemorrhage. Ganglia and nerve fibers were heavily infiltrated with CD4+ T cells and CD8+ T cells. Moreover, upregulation of the expression of the major histocompatibility complex MHC-I and MHC-II molecules was observed on glial cells. The more severe pain in the acute phase represents a more severe inflammatory response and nerve fiber damage and destruction, thus the more obvious signs and symptoms of neuralgia appear (9).

The Calca gene encodes 2 polypeptides, calcitonin (CT) and calcitonin gene-related peptide (CGRP) (10). CT is a hormone produced primarily by thyroid C cells and is thought to be a major regulator of bone resorption (10), while CGRP is a neuropeptide expressed in cells of the central and peripheral nervous system and is thought to be associated with pain (11). Guedon et al (12) used HZ virus infection in rats and found that the expression of nociceptive genes neurotrophic receptor tyrosine kinase 2 (NTRK2), transient receptor potential vanilloid 1 (TRPV1), and CGRP were modulators of these genes. Continuous infiltration of inflammatory factors induces abnormal opening and high expression of several ion channels, such as calcium and sodium, which promotes neurotransmitter release and contributes to the reorganization of central neuroreceptors, further aggravating central sensitization and leading to a chronic course of the disease (13) and the formation of PHN.

The use of antiviral drugs was also found to be one of the risk factors affecting the development of PHN in patients with postmalignancy HZ. The difference was statistically significant ($P < 0.05$) between 21.2% (7/33) of the group administered 2 antiviral drugs and 66.7% (4/6) of the group not administered antiviral drugs. That is, the use of antiviral drugs in adequate doses early in the acute phase reduces the incidence of PHN.

Antiviral drugs are commonly used in the clinical treatment of HZ (14), and early and adequate antiviral therapy is similarly recommended for patients with postmalignancy HZ, which can effectively shorten the course of the disease and accelerate the healing of the rash. It is currently believed that PHN occurs in approximately 9% to 34% of patients with HZ (7). Viral replication is an important link in the development of the disease: the posterior horn of the posterior nerve root and ganglion are involved, triggering intense and limited inflammation of the nerve tissue; the virus migrates along the sensory nerves to the corresponding skin mucosa, promoting an inflammatory response of the skin and mucosa. Therefore, early, regulated, and adequate use of antiviral drugs can effectively inhibit viral DNA polymerase, prevent the extension of the DNA replication chain, reduce the neuroinflammatory response and decrease the incidence of PHN (7).

In terms of reducing prevalence, Mullane, et al (15) used inactivated VZV vaccine in patients who were immunocompromised and were being treated with chemotherapy for a solid tumor malignancy to effectively prevent HZ; the hematologic malignancies arm was

Table 2. *Assignment of independent variables.*

Variables	Assignment
Age (years)	< 60 years = 1, ≥ 60 years = 2
Tumor TNM Staging	Stage I = 1, Stage II= 2, Stage III = 3, Stage IV = 4
Acute phase NRS Score	≤ 3 points = 1, 4~6 points = 2, ≥ 7 points = 3
Antiviral drugs	No antiviral use = 1, Single antiviral =2, 2-combination antiviral = 3
Chemotherapy	No chemotherapy = 0, chemotherapy = 1
Radiation Therapy	No radiotherapy = 0, radiotherapy = 1
Surgical treatment	No surgery = 0, surgery = 1

Table 3. *Logistic regression analysis results of influencing factors of PHN in HZ postmalignancy.*

Variables	Regression coefficient	Standard error	Wald χ^2 value	*P* value	Odds Ratio value	95% CI
Age (years)	-0.534	0.685	0.608	0.435	0.586	(0.153-2.243)
Acute phase NRS-11 Score	1.439	0.501	8.266	0.004	4.218	(1.581-11.252)
Antiviral drugs	-1.251	0.538	5.410	0.020	0.286	(0.100-0.821)
Tumor TNM Staging	-1.267	0.639	3.928	0.047	0.282	(0.081-0.986)
Chemotherapy	1.149	0.735	2.446	0.118	3.155	(0.748-13.313)
Radiation Therapy	-0.254	0.938	0.073	0.787	0.776	(0.123-4.878)
Surgical treatment	0.418	0.725	0.332	0.565	1.518	(0.367-6.287)
Constants	1.616	2.108	0.588	0.443	5.035	

terminated early. None of the patients analyzed in our review had received the HZ vaccine; perhaps more studies are needed for future HZ vaccine administration in these specific populations.

The tumor stage was found to be one of the risk factors affecting the development of PHN in patients with postmalignancy HZ. TNM is the staging of cancer by summarizing the degree of malignant tumor progression in the order of tumor size or extension (T), regional lymph node involvement (N) and distant metastasis (M), which to some extent reflects disease severity (16). Wu et al (17), based on the tumor microenvironment to predict the overall survival of lung adenocarcinoma patients, found that higher tumor microenvironment risk scores were negatively correlated with the abundance of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and other stromal cells or immune cells. In the subgroup analysis of TNM staging, higher tumor microenvironmental risk scores were considered to be a poor factor for overall survival. This means that patients with malignant tumors with a higher TNM stage have abnormal changes in the body's immune microenvironment and are more prone to bacterial and viral infections. Patients with acute-stage HZ will have fewer immune cells in the broken skin tissue, which in turn leads to a weakened effective suppression of the HZ virus and increased damage to skin segments, resulting in persistent neuralgia and eventual progression to PHN.

Age (≥ 60 years) was an influential factor in the occurrence of PHN when the univariate analysis was performed in our study. The multifactorial logistic regression analysis showed no difference with a *P* value greater than 0.05, which was not statistically significant. However, some studies have shown that PHN occurs in middle-aged and elderly patients, with HZ affecting those older than 50 years with a mean incidence of 14.33% (18). Forbes et al (6) pointed out that age is a recognized risk factor for the development of the disease. Immune senescence occurs in elderly patients with age, and as present study was based on malignant tumor patients, declined cellular and humoral immune functions were observed (19). These conditions could cause the spread of viral infection, severe neurological damage and a weaker ability to repair neurological damage in the elderly in comparison to the young, thereby resulting in a high incidence of PHN.

Elderly patients in this study were defined as those aged ≥ 60 years. Chemotherapy (20), radiotherapy (21), and surgical treatment can damage the immune system to varying degrees while fighting against tumors, leading to the occurrence of opportunistic infections. However, age was not found to be an influential factor in the occurrence of PHN through this study, which may be related to the group we studied, where malignancies are more concentrated in older age groups.

Another study (22) showed the presence of anterior pain and a large skin lesion in the acute phase as risk factors for the occurrence of PHN. This study was retrospective and the description of the nature of the pain in the medical records was incomplete; the nerves involved in the acute phase were not recorded according to the distribution of the neurocutaneous ganglion, so the above 2 factors were not included in the analysis (20).

Limitations

There are some limitations in our research, such as its being conducted at a single center, with a single race, and had a small sample size. A larger scale study should be conducted to analyze the influencing factors of PHN in patients with postmalignancy HZ.

Conclusion

In conclusion, HZ is prone to occur during the treatment of patients with a malignancy. Our study found that the degree of pain in the acute phase of HZ, the use of antiviral drugs, and the tumor stage are influential factors in the occurrence of PHN. Early, adequate, and standardized administration of antiviral therapy in patients with postmalignancy HZ should reduce the occurrence of PHN. Potential infectious diseases such as HZ should be monitored for throughout the treatment of patients with a malignancy, and collaboration among oncology, pain medicine, and dermatology should be strengthened for early detection, diagnosis, and treatment.

Author Contributions

HL-L participated in data collection and drafted the article. GG-G and JL-W performed the literature search, data acquisition, and analysis. FB-L had the idea for the study and critically revised the work. All authors contributed to the article and approved the submitted version.

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