J Med Sci 2020;40(1):42-45
DOI:10.4103/jmedsci.jmedsci_86_19

CASE REPORT

Paraneoplastic Leukemoid Reaction Associated with Poor Prognosis in Oral Squamous Cell Carcinoma: A Case Report and Literature Review

Li-Tsun Hsieh[1], Chien-Liang Lin[2], Yu-Kang Chang[3], Sheng-Yow Ho[1,4]

Departments of [1]Radiation Oncology and [2]Hematology Oncology and [3]Diagnostic Radiology, Chi Mei Medical Center, Liouying, [4]Graduate Institute of Medical Science, Chang Jung Christian University, Tainan, Taiwan

Paraneoplastic leukemoid reaction (PLR) is exceedingly uncommon syndrome in oral cancer and has implicated a worse outcome. This report describes a case of buccal mucosa cancer encountered PLR syndrome during the course of tumor progression. We conduct a literature review to highlight the relationship between PLR and the outcome in oral cancer. PLR is associated with rapid tumor growth and worse outcome in head-and-neck cancer.

Key words: Extreme leukocytosis, oral cancer, paraneoplastic leukemoid reaction, prognosis

INTRODUCTION

Leukemoid reaction (LR) is a hematological disorder in response to severe infection, intoxications, severe hemorrhage, acute hemolysis, or other marrow stimulants. It is defined by marked leukocytosis with a significant increase in neutrophils or its precursor cells.[1]

Paraneoplastic syndromes are a group of clinical symptoms caused by certain cancers and not directly attributed to local tumor infiltration or metastatic spreading. The syndrome is associated with the secretion of functional hormones or cytokines from the tumor. Paraneoplastic LR (PLR) is a rare syndrome in patients with malignancies. It indicates a negative prognosis, leading to a higher rate of recurrence and distant metastases.[2-8]

Oral cancer is the sixth most common cancer in Taiwan. More than 7800 cases are reported in the 2016 Cancer Registry.[9] PLR in oral cancer is an exceedingly uncommon syndrome.

This report describes a case of buccal mucosa squamous cell carcinoma (SCC) with extreme PLR, more than 50×10^3 cells/μL, during the course of tumor progression. We also conduct a review using Medline to highlight the poor outcome of head-and-neck cancer with PLR in the literature.

Received: May 02, 2019; Revised: June 12, 2019; Accepted: August 13, 2019; Published: October 11, 2019
Corresponding Author: Dr. Sheng-Yow Ho, Department of Radiation Oncology, Chi Mei Medical Center, Liouying, 201, Taikang, Liouying, Tainan 73657, Taiwan. Tel: +886-6-6226999 ext. 71010; Fax: +886-6-6220226. E-mail: shengho@seed.net.tw

CASE REPORT

A 49-year-old male presented with a painful ulcerated mass at the left buccal mucosa for several months came to our hospital in December 2017. Left buccal mucosa SCC was confirmed through incision biopsy. Magnetic resonance imaging (MRI) and positron emission tomography (PET) showed a localized disease without systemic metastases. The initial laboratory data only revealed mild leukocytosis without immature cells. His white blood cell (WBC) count was 11.4×10^3 cells/uL (reference: $3.4–9.1 \times 10^3$). The patient received wide excision of the tumor and bilateral supraomohyoid neck dissection on December 27, 2017. The pathology report confirmed a 3-cm tumor with well-differentiated SCC and no metastatic neck lymph node. The pathologic stage was T2N0 according to the 7th edition staging system of the American Joint Committee on Cancer. The only risk factor for adjuvant radiotherapy was a close surgical margin of 0.3 cm. The peripheral blood leukocyte counts were within normal values during the course of radiotherapy.

How to cite this article: Hsieh LT, Lin CL, Chang YK, Ho SY. Paraneoplastic leukemoid reaction associated with poor prognosis in oral squamous cell carcinoma: A case report and literature review. J Med Sci 2020;40:42-5.

Follow-up MRI found a relapsed tumor in the left submandibular region only 1 month after adjuvant therapy [Figure 1a] and confirmed recurrent SCC by tumor extirpation. Repeated tumor workup, including PET scan and image studies, all reported localized relapse only. However, his WBC count elevated to 14.8 × 10^3 cells/uL without any evidence of infection. Docetaxel, cisplatin, and fluorouracil were prescribed as salvage treatment from June 2018. Cetuximab was added to counter rapid proliferation in July 2018. Progressive tumor disease was evident during the salvage chemotherapy and cetuximab treatment. WBC counts were within relatively normal values during the salvage course (in the range of 4.9–13.4 × 10^3 cells/uL). He did not develop the episode of leucopenia during the salvage treatment from July to August. The tumor spread rapidly to the masticator space, tongue base, and hypopharynx in September 2018 [Figure 1b]. While the tumor progressed rapidly, his WBC count abruptly elevated up to a value of 52.8 × 10^3 cells/uL, with 95% mature neutrophils and without any immature bands, myelocytes, or meta-myelocytes. The time course of WBC counts after recurrence was shown in Figure 2. He had no signs of infection or fever during extreme leukocytosis. Serial septic examinations, including chest X-ray, urine culture, and blood cultures, were all negative.

Pembrolizumab was prescribed for the attempt to attenuate tumor progression in mid-October 2019. His WBC count decreased to 33 × 10^3/uL first and then increased up to 60–70 × 10^3/uL at the end of October. The tumor had no sign of regression in the event of the transient drop of WBC count. During the last month of admission, the WBC counts still remained high at around 68–95 × 10^3/uL. The patient succumbed to respiratory failure at the end of November, 2018.

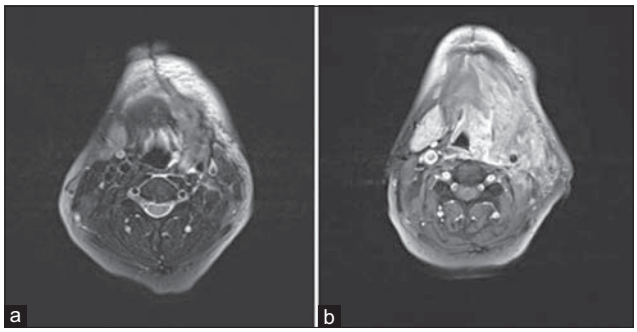

Figure 1: (a) Magnetic resonance imaging finding of local recurrence following radiotherapy and confirmed recurrent tumor by tumor extirpation. (b) Rapid progression only 3 months after salvage chemotherapy

DISCUSSION

The mechanism of PLR is caused by the production of functional hormones or cytokines by the tumor. Such high level of WBC count is thought to be attributable to tumor secretion of granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or interleukin-6, and however, serum levels of these functional cytokines were not confirmed in our patient due to lack of routine laboratory examinations. The syndromes may represent the earliest sign of an occult malignancy and could be an indicator of prognosis.[1] In this case, the patient experienced extreme leukocytosis while the tumor progressed. Serial hemograms showed <90% mature neutrophils and no immature granulocytes. The extreme leukocytosis in our case might not due to acute infection owing to lack of clinical infection symptoms and signs. Regrettably, our evaluation for PLR was not fulfilled on the exclusion of hematologic malignancy. Moreover, in view of the poor performance of our case, we did not perform a bone marrow aspiration or biopsy and cytogenetic study to rule out any possibility of myeloproliferative neoplasms. Hence, hematologic malignancy could not be totally excluded only by the hematological manifestation.

PLR is extremely rare in solid tumors. Its incidence is not well documented. This syndrome indicates a poor prognosis in the literature.[2-6] Although plenty of studies point out leukocytosis is a poor prognostic factor in patients with malignant disease, it is not clear if the severity of leukocytosis is correlated to worse survival. Chen *et al*. concluded the occurrence of leukocytosis (WBC >15 × 10^3 cells/uL) in oral SCC during

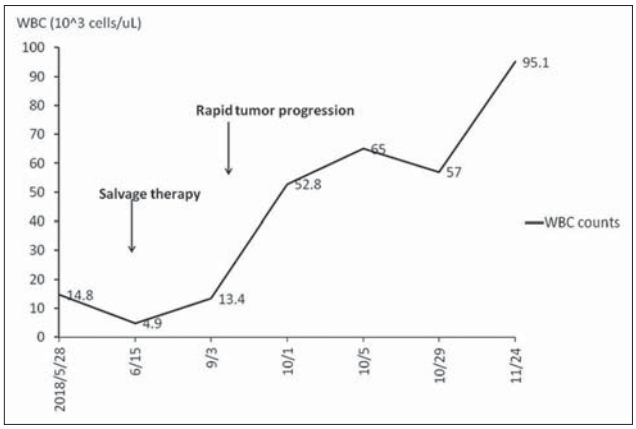

Figure 2: The time course of leukocyte counts following the recurrence of oral carcinoma. The leukocyte counts increased paralleling with the growing tumor, ranging from 52.8 to 95.1 × 10^3/uL (reference: 3.4–9.1 × 10^3)

Table 1: Literature review on leukemoid reaction and head-and-neck cancer

Study (references)	Tumor sites	Age (years)	Pathology	Primary therapy	Recurrence or metastasis	Peak of WBC count (10^3 cells/uL)	Survival (months)
Yoneda *et al*. (1989)[2]	Maxillary sinus	52	SCC	OP	Yes	172	10
Yoneda *et al*. (1989)[2]	Tongue	41	SCC	RT, CT	Yes	180	4
Yoneda *et al*.[5]	Maxillary	82	Adenocarcinoma	CT, OP	Yes	60	60
Horii *et al*.[8]	Tongue	61	SCC	OP	Yes	96.2	12
Our report	Buccal	49	SCC	OP, RT	Yes	95	11

SCC=Squamous cell carcinoma; OP=Operation; CT=Chemotherapy; RT=Radiotherapy; WBC=White blood cell

the course of the therapy adversely impacts survival.[4] Granger and Kontoyiannis enrolled 758 cancer patients with extreme leukocytosis (WBC >40 × 10^3 cells/uL) during cancer therapy. In these 758 leukocytosis patients, only 77 (10%) patients could be categorized as PLR and 54 (86%) of those with PLR died within 3 months. Only one head-and-neck cancer patient was identified in the group of PLR.[7] To highlight the unique syndrome in head-and-neck cancer, we conducted a literature review to identify the relationship between extreme PLR and outcome. Databases of Medline and PubMed were searched. Case reports describing a prognosis of head-and-neck cancer experiencing extreme PLR are listed in Table 1. Only four head-and-neck cancers associated with extreme PLR were reported, and none of them mentioned buccal cancer. In our case, his WBC count increased paralleling with the growing tumor. Most malignant head-and-neck tumors with PLR responded poorly to therapy. Most patients die within 1 year after the occurrence of PLR.[2,5,8,10]

Granger and Kontoyiannis reported PLR patients who survived longer than 1 year only following effective antineoplastic therapy.[7] Most malignant tumors with PLR respond poorly to management. In our case, we used different chemotherapy regimens and immunotherapy to attenuate the tumor progression. Nonetheless, the patient died soon despite aggressive salvage therapy.

In conclusion, PLR is often associated with rapid tumor growth and worse outcome in head-and-neck cancer.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient's familyconsent forms. In the form the patient's family has given their consent for his images and other clinical information to be reported in the journal. The patient's family understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sakka V, Tsiodras S, Giamarellos-Bourboulis EJ, Giamarellou H. An update on the etiology and diagnostic evaluation of a leukemoid reaction. Eur J Intern Med 2006;17:394-8.
2. Yoneda T, Nishikawa N, Nishimura R, Kato I, Sakuda M. Three cases of oral squamous cancer associated with leukocytosis, hypercalcemia, or both. Oral Surg Oral Med Oral Pathol 1989;68:604-11.
3. Schernberg A, Moureau-Zabotto L, Campo ER, Escande A, Ducreux M, Nguyen F, *et al.* Leukocytosis and neutrophilia predict outcome in locally advanced esophageal cancer treated with definitive chemoradiation. Oncotarget 2017;8:11579-88.
4. Chen YW, Chen IL, Lin IC, Kao SY. Prognostic value of hypercalcaemia and leucocytosis in resected oral squamous cell carcinoma. Br J Oral Maxillofac Surg 2014;52:425-31.
5. Yoneda T, Nishimura R, Kato I, Ohmae M, Takita M, Sakuda M, *et al.* Frequency of the hypercalcemia-leukocytosis syndrome in oral malignancies. Cancer 1991;68:617-22.
6. 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.
7. Granger JM, Kontoyiannis DP. Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: A retrospective, single-institution study. Cancer 2009;115:3919-23.

8. Horii A, Shimamura K, Honjo Y, Mitani K, Miki T, Takashima S, *et al.* Granulocyte colony stimulating factor-producing tongue carcinoma. Head Neck 1997;19:351-6.
9. Cancer of oral cavity In: Taiwan Cancer Registry Annual Report; 2016. Health Promotion Administration, Ministry of Health and Welfare Taiwan 2018, p. 6-14.
10. Kuş AB, Şahin P, Uğuz AH, Tanyeli A, Küpeli S. Leukemoid reaction associated with pediatric nasopharyngeal carcinoma: An unusual presentation. Int J Pediatr Otorhinolaryngol 2014;78:885-7.