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ORIGINAL ARTICLE

Pretreatment thrombocytosis

A prognostic marker for oral squamous cell carcinoma?

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Abstract
Purpose Thrombocytosis associated with poorer prognoses seems to be a frequent preoperative finding in different kind of cancers. The aim of the present study was to evaluate whether thrombocytosis can be used as a prognostic marker for oral squamous cell carcinoma (SCC).
Methods Altogether, 288 patients with oral SCC were considered, as well as all platelet counts between 1 and 5 days prior to surgical treatment, recurrence rate, and lymph node metastasis. The minimum follow-up time was 12 months.
Results The mean preoperative thrombocyte score of the patients who received surgery was 259.55±83.8 Tsd/μl; 273 out of 288 patients were in the normal thrombocyte range, and 12 had a thrombocytosis. From 51 patients with recurrence, three were in the thrombocytosis group, and 45 patients with recurrence were in the normal thrombocyte range.
Conclusion The present results do not confirm that thrombocytosis can be seen as marker for poor tumor prognosis.

Keywords Thrombocytosis · Head and neck cancer · Prognosis · Oral squamous cell carcinoma

Introduction

The 5-year survival rate for oral squamous cell carcinoma (SCC) has been virtually unchanged over the past few decades. Several prognostic factors—like infiltration depth, metastases, and perineural infiltration [1]—are well known. Concerning the markers in the routine laboratory test for oral SCC, a few studies have been performed concerning CRP [2] and haemoglobin [3]. Thrombocytosis, which is an abnormally high number of platelets in the circulating blood, in association with malignancies was described by Riess in 1872 [4]. More recently several studies have reported thrombocytosis as associated with renal [5], colorectal [6], endometrial [7], breast [8], gastric [9], lung [10], and esophageal cancers [11]. However, for oral SCC only one study, to the authors' knowledge, has reported an association for oral cancer [12] in 253 patients with a poorer survival rate, aggressive tumor growth, lymph node metastases, and distant metastases.

Therefore, the aim of the current study was to evaluate the prevalence of thrombocytosis and its association with recurrence and metastases rates.

Patients and methods

A total of 311 patients who were treated for oral SCC between 1999 and 2008 at a single center (Department of Craniomaxillofacial and Oral Surgery, University Hospital, Zurich) were evaluated retrospectively. All platelet counts between 1 and 5 days prior to surgical treatment, recurrence rate, and lymph node metastasis were taken into consideration. An Excel database was used for evaluation. The minimum follow-up time was 12 months. Exclusion criteria were inadequate information, a follow-up time of less than 12 months, autoimmune disease, acute inflammatory disease, and haemodialysis. Therefore, two male patients were excluded: one due to Fanconi Anemia and the other

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because of a graft-versus-host disease after stem cell transplantation.

In agreement with other studies [13, 14], we defined a thrombocytosis as >400,000 thrombocytes/μl.

Results

Between 1998 and 2008, oral cancer was detected in 309 patients in the Department of Cranio-Maxillo-Facial Surgery of the University Hospital in Zurich. Of these patients, 21 (6.8%) were treated with primary radiotherapy. The other 288 patients (93.2%) received surgery with or without radiotherapy/chemotherapy.

The mean preoperative thrombocyte score of the patients who received surgery was 259.55±83.8 Tsd/μl. In 273 patients (94.8%), the preoperative score was under 400 Tsd/μl, and in 259 patients (89.9%) the score was in the normal range between 150 and 400 Tsd/μl. Twelve patients (4.2%) had an elevated thrombocyte score over 400 Tsd/μl, and no preoperative score was documented for three patients (1%) (Fig. 1).

Local recurrence was seen in 51 patients (17.7%) after a mean time of 23.73±23.78 months (range 1–89 months). The occurrence of second tumors was seen in 21 patients (7.3%) after a mean time of 27.71±18.17 months (range 4–87 months). No recurrence or occurrence of second tumors was seen in 216 patients (75%). Cervical lymph node metastases were observed in 45 patients (15.6%) after a mean time of 16.71±23.09 months (range 1–93 months), and distant metastases were detected in 19 patients (6.6%) after a mean time of 23±24.45 months (range 2–111 months). No metastases were found in 224 patients (77.8%).

Table 1 Overview of the studied patient

	150,000–400,000 (Normal range)	>400,000 Elevated group)
Patients	273 patients	12 patients
Recurrence	48 patients	3 patients
Metastases	45 patients	0 patients
Second tumor	17 patients	4 patients

A local recurrence was observed in 48 patients (94.1%) in the normal range group and in three patients (5.9%) in the group with elevated preoperative Tc scores. No correlation was found between tumor recurrence and the preoperative Tc score. All 17 patients who developed a second tumor had a normal preoperative Tc score. Nor were preoperative thrombocyte counts (Table 1) found to relate time elapsed before recurrence (Fig. 2) or before metastases (Fig. 3). All 45 patients with lymph node metastases were in the group with a normal Tc score.

Discussion

Thrombocytosis associated with poorer prognoses has seemed to be a frequent preoperative finding in different kind of cancers, and the development of thrombi accompanying cancer cells has been well studied. However, our study did not support the notion that thrombocytosis is associated with a

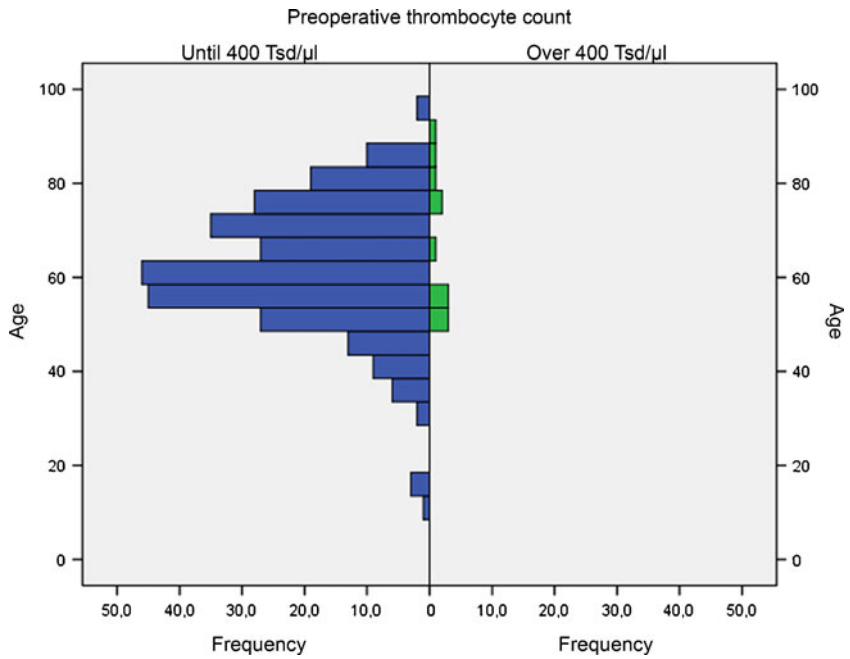

Fig. 1 Overview of the thrombocyte count in the patients studied

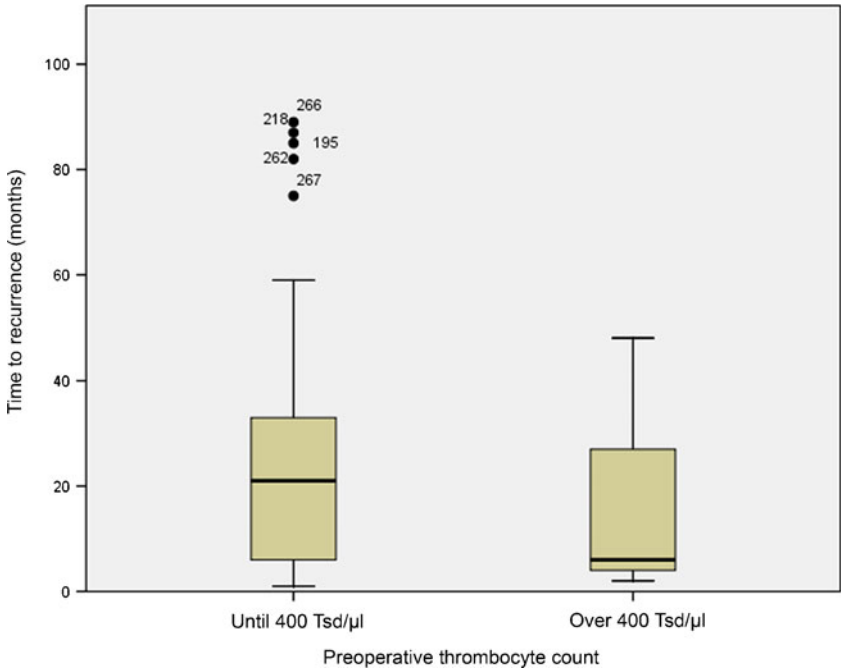

Fig. 2 Time to recurrence

higher recurrence and metastases rate. One reason could be that most oral cancer metastasis occurs by lymphatic spread instead of through hematologic spread, and platelets appear to contribute to metastasis haematologically spread by their adhesive interaction with tumor cells via the adhesive proteins fibronectin and von Willebrand factor [15]. The ability of some tumor cells to aggregate platelets in vitro and their metastatic potential in vivo is well known [16]. It would be of interest to investigate whether oral SCC cell lines do have this ability. Therefore, further investigation is still needed.

In the present study, thrombocytosis was found in 4.2% patients with oral SCC. This is considerably lower than the results (61 out of 253 patients/24.1%) reported by Lu et al. [12]. Lu et al. [12] proposed that preoperative thrombocytosis could be associated with a larger tumor burden or a later stage, both of which adversely affect survival. The

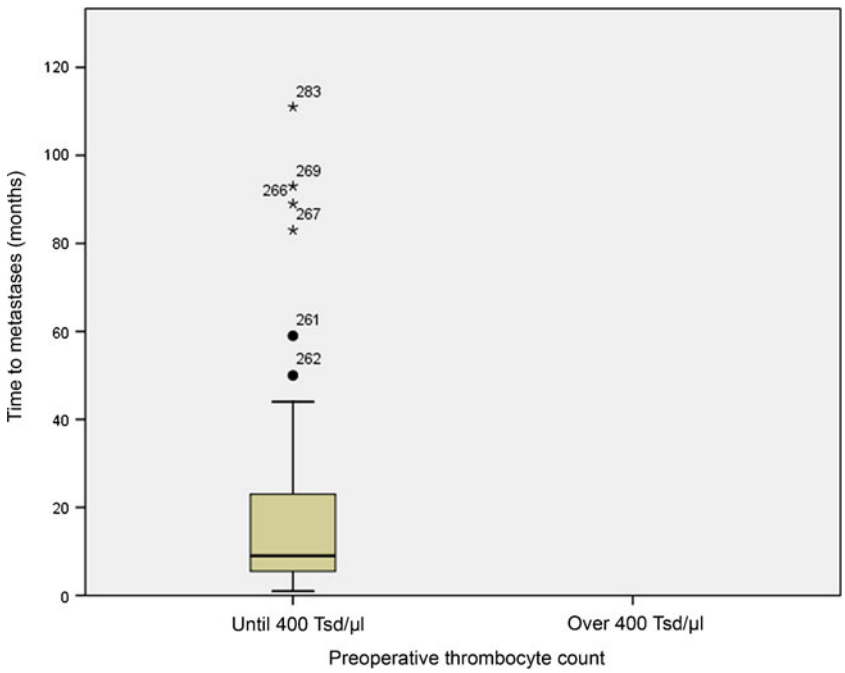

Fig. 3 Time to metastases

prevalence reported in studies of other malignancies ranged from 4.5% [17] to 25% [18].

The pathophysiology underlying the reactive thrombocytosis in patients with malignoma has yet not been fully elucidated. An increase of tumor-related humoral factors leading to an increased production of platelet, as well as tumor-derived factors with thrombopoietin-like activity and growth factors in addition to growth factors released by megakaryocytes, are believed to influence this process [19, 20]. In inflammatory conditions, a stimulation of interleukin-6 (IL-6), a potent stimulator of megakaryocytopoiesis, leading to increased thrombopoietin has been reported [21]. It is also unclear whether thrombocytosis is a result of growth factors secreted by tumor cells and the host response, or an event that directly worsens the prognosis [17]. The other question that still has not been solved is whether hypoxy plays a stimulating role in thrombocytes, as it does in erythrocytes [22]. Vascular endothelial growth factor (VEGF), known to be increased in hypoxic tissue, is also released by platelets on activation, and VEGF seems to correlate with the platelet count [23], leading also to an increased number of blood vessels in tumors.

These data, which are limited by the retrospective nature of the study, do not confirm a causal relationship between tumor aggressiveness and thrombocytosis.

Conflict of interests The authors declare that they have no competing interests.

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