The postoperative fall in platelet count in cancer: Mirroring the catastrophe?

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Abstract

Introduction: Progression of cancer requires the growth and invasion of the tumor at its parent site as well as metastasis. Recent studies have shown that tumor cells can aggregate platelets in vitro (a process termed tumor-cell-induced platelet aggregation [TCIPA]), and this aggregation correlates with the metastatic potential of cancer cells in vivo. Platelet depletion or even an inhibition of TCIPA reliably diminishes metastasis. Furthermore, tumor cells bind platelet adhesion receptors of circulating platelets to metastasize more effectively. Studies say that malignant tumors to interact with platelets in the above fashion secrete platelet activating factors which raise the platelet count in malignancy. The study undertaken aims at comparing the preoperative and postoperative platelet levels in patients with benign and malignant neoplasms.

Materials and Methods: With an appropriate sample size of patients with benign or malignant neoplasms as per the inclusion and exclusion criteria, a platelet count presurgically and the 7th day postsurgically was advised.

Results: In case of patients with benign neoplasms, the postoperative platelet count showed a significant rise attributed to a normal healing response, while in patients with malignant neoplasms, the platelet count appeared to fall down significantly due to the effect of tumor removal and therefore a diminished production of thrombopoietic cytokines. The results obtained were thus consistent with the theories of tumor cell-platelet interactions proposed in the recent literature so far.

Conclusion: Postoperatively, the platelet count rises in the patients with the benign tumor as a result of a normal healing response while those in patients with malignant neoplasm apparently appears to fall down due to the effect of tumor removal thus diminishing the production of platelet activating factors.

Keywords: Benign neoplasms, malignant neoplasms, metastasis, platelets

INTRODUCTION

Platelets have been known to us since eras as one of the major cellular fragments in the circulating blood, performing their chief function of forming the primary hemostatic plug; later providing a surface for the coagulation factors to form the secondary hemostatic plug and ultimately maintaining surveillance in the blood vessel continuity.[1] Thus, this is an obvious “life-saving” role of platelets.
However, in the recent past, a darker side of platelets has also come into play, and that is, their role in cancer progression. Various research studies have identified platelets as one of the role players in the spread and progression of cancer, by helping the cancerous cells to evade the immunity and metastasize.\[2\]

Despite the major advancements in the basic biology of cancer and the novel therapeutic implications, cancer remains as one of the deadliest threats to humanity. Thus, every factor that has been implicated or is supposed to be implicated in the progression of this disease is needed to be studied further in depth for the likelihood of developing better curative measures.

So, taking into consideration the need to work against deadly cancers and the role being played by platelets in the spread and progression of such cancers,\[2,3\] the following study was undertaken wherein the platelet counts were compared preoperatively and postoperatively in patients with benign and malignant neoplasms.

MATERIALS AND METHODS

The study population included patients who were histopathologically confirmed to have either a benign neoplasm or a malignant neoplasm, with no history of ecchymosis and petechiae on general physical examination and admitted for a surgical interventional therapy with no history of adjunctive chemotherapy or radiotherapy. Care was taken to exclude those patients who were transfused blood before, during or after the surgery that would result in a false platelet count. Also were excluded those patients who were under medications that would have in any way altered the level of platelets in the circulating blood. Other factors such as the half-life of the postsurgical medications and their any possible effect on platelet counts were also taken into consideration, and the patients who were on prolonged postsurgical drugs that would have altered or affected the platelet counts were also excluded from the study. Thus, overall care was taken to include only those patients who were relieved of all the confounding factors.

The sample size was calculated using the Online OpenEpi Software Version 3.03a (Aurangabad, India), and 48 patients who met the above inclusion and exclusion criteria were selected for the study. Among these, 16 patients were diagnosed with a benign neoplasm and 32 with a malignant neoplasm.

The patients in the study group were advised to undergo a platelet count 2–3 days before the surgery and 7th day postsurgically. During the entire span of the study, the same Cell Counter was used for all the patients to avoid any technically induced deviations in the platelet counts. These counts were recorded and computed, and a paired t-test with the help of Online GraphPad Software was applied to the data generated for both the benign and malignant neoplasm patients. The comparison was made between the preoperative and postoperative platelet counts in both the independent groups of benign and malignant neoplasms.

The study was approved by the Institutional Ethical Committe, and a written informed consent was obtained from all the patients included in the study.

RESULTS

The mean preoperative platelet count was 297.75 K/µl and the mean postoperative platelet count was 187.15 K/µl in patients with malignant neoplasm [Table 1] while in patients with benign neoplasm, the mean preoperative platelet count was 207.25 K/µl and the mean postoperative platelet count was 264.25 K/µl [Table 2] the difference in the pre-operative and the post-operative levels being statistically significant ($P < 0.0001$) in both the cases [Table 3 and Figure 1].

From the above-obtained results, it was evident that there was a rise in the platelet count postoperatively in patients with benign neoplasm while a fall in those with malignant neoplasm. The reason behind both the phenomenon can be justified as follows.

DISCUSSION

In normal physiology, the platelet count is maintained at a particular required level with the help of thrombopoietic cytokines and remains unaltered unless there is a disease or

![Figure 1: Difference in the mean platelet counts in malignant and benign neoplasm](image-url)
In case of malignant neoplasm, the malignant cells themselves secrete these thrombopoietic cytokines, and their levels are thus higher in malignant neoplasm patients. These higher levels of thrombopoietic cytokines thus result in increased production of platelets. Thus after the resection of the tumor, the part of thrombopoietic cytokines that were being secreted by the tumor cells fall, and subsequently, there is reduction in the production of platelets. This gives an impression of falling count of platelets postoperatively.

The raised levels of platelets preoperatively in malignant neoplasm conditions help in cancer progression by the following mechanism.

**Formation of tumor-cell-induced platelet aggregates**

As early as in 1968, it had been suggested that platelets bind to tumor cells to form tumor-cell-induced platelet aggregates (TCIPA) and later, it had been recognized that these TCIPA help in tumor metastasis. The various platelet receptors that are involved in the hematogenous spread of tumor cells are GPIb-IX-V, GPVI, Integrin α2β1, adenosine diphosphate receptor, P-selectin, and thrombin receptors (protease-activated receptors). These receptors bind to the mucin and other corresponding molecules that are expressed by the tumor cells to bind them and form TCIPA. The formation of these TCIPA offer advantages to the tumor cells by shielding them from the immune system.

### Table 1: The preoperative and postoperative platelet counts in patients with malignant neoplasm

| Serial number | Malignant neoplasm           | Preoperative platelet count (K/µl) | Postoperative platelet count (K/µl) |
|---------------|------------------------------|-----------------------------------|-----------------------------------|
| 1             | SCC pterygomandibular raphe  | 280                               | 132                               |
| 2             | Malignant melanoma           | 262                               | 152                               |
| 3             | SCC lower lip                | 271                               | 149                               |
| 4             | SCC gingival                 | 295                               | 171                               |
| 5             | SCC buccal mucosa            | 335                               | 169                               |
| 6             | SCC palate                   | 301                               | 174                               |
| 7             | SCC floor of mouth           | 291                               | 151                               |
| 8             | Osteosarcoma ramus           | 333                               | 178                               |
| 9             | SCC buccal muosa             | 308                               | 164                               |
| 10            | SCC buccal vestibule         | 342                               | 230                               |
| 11            | SCC lateral border of tongue | 269                               | 149                               |
| 12            | SCC lateral border of tongue | 276                               | 135                               |
| 13            | Malignant melanoma           | 345                               | 158                               |
| 14            | SCC buccal mucosa            | 329                               | 136                               |
| 15            | Basaloid SCC                 | 299                               | 150                               |
| 16            | SCC lateral border of tongue | 301                               | 171                               |
| 17            | SCC buccal vestibule         | 260                               | 189                               |
| 18            | SCC buccal mucosa            | 361                               | 155                               |
| 19            | SCC lateral border of tongue | 342                               | 201                               |
| 20            | Basal cell carcinoma         | 329                               | 194                               |
| 21            | SCC floor of mouth           | 315                               | 175                               |
| 22            | SCC buccal vestibule         | 342                               | 267                               |
| 23            | SCC buccal mucosa            | 376                               | 243                               |
| 24            | SCC buccal mucosa            | 264                               | 202                               |
| 25            | SCC floor of mouth           | 301                               | 262                               |
| 26            | SCC buccal vestibule         | 212                               | 174                               |
| 27            | SCC lower lip                | 297                               | 164                               |
| 28            | SCC palate                   | 278                               | 178                               |
| 29            | SCC buccal muosa             | 234                               | 210                               |
| 30            | SCC buccal mucosa            | 262                               | 201                               |
| 31            | SCC lateral border of tongue | 220                               | 178                               |
| 32            | SCC lateral border of tongue | 298                               | 141                               |
| **Mean±SD**   |                              | **297.75±39.59**                   | **187.15±34.75**                   |

SD: Standard deviation, SSS: Squamous cell carcinoma

### Table 2: The preoperative and postoperative platelet counts in patients with benign neoplasm

| Serial number | Benign neoplasm              | Preoperative platelet count (K/µl) | Postoperative platelet count (K/µl) |
|---------------|------------------------------|-----------------------------------|-----------------------------------|
| 1             | Lipoma                       | 241                               | 252                               |
| 2             | Auricular chondroma          | 223                               | 249                               |
| 3             | Adenoma thyroid              | 278                               | 342                               |
| 4             | Leiomyomyma                  | 196                               | 241                               |
| 5             | Uterine fibroid              | 210                               | 263                               |
| 6             | Osteoma                      | 241                               | 268                               |
| 7             | Plexiform fibroma            | 164                               | 158                               |
| 8             | Osteoblastoma                | 198                               | 246                               |
| 9             | Fibroma                      | 236                               | 223                               |
| 10            | Ameloblastoma                | 267                               | 340                               |
| 11            | Lipoma                       | 230                               | 318                               |
| 12            | Osteoma                      | 199                               | 286                               |
| 13            | KCOT                         | 145                               | 256                               |
| 14            | Fibroma                      | 165                               | 278                               |
| 15            | Lipoma                       | 178                               | 243                               |
| 16            | Lipoma                       | 145                               | 265                               |
| **Mean±SD**   |                              | **207.25±40.82**                   | **264.25±44.80**                   |

SD: Standard deviation, KCOT: Keratocystic odontogenic tumor

a greater demand. In case of malignant neoplasm, the malignant cells themselves secrete these thrombopoietic cytokines, and their levels are thus higher in malignant neoplasm patients. These higher levels of thrombopoietic cytokines thus result in increased production of platelets.
Table 3: Statistical analysis of the difference in the mean platelet counts in benign and malignant neoplasms

| Nature of the tumor | Mean preoperative platelet count (K/µl) | Mean postoperative platelet count (K/µl) | P    | t    |
|---------------------|----------------------------------------|------------------------------------------|------|------|
| Malignant           | 297.75±39.59                           | 187.15±34.75                            | <0.0001 | 14.5498 |
| Benign              | 207.25±40.82                           | 264.25±44.80                            | <0.0001 | 5.5138  |

from recognition by the immune system. The aggregate that forms around the tumor cells thus prolongs their survival in the circulation by checking the attack of natural killer (NK) cells over them and preventing the lysis of the tumor cells. In addition recently, it has been proposed that platelet-derived transforming growth factor-β, secreted on platelet activation by tumor cells, down-regulates the activating immunoreceptor NKG2D on NK cells. Secondly, these TCIPAs contain activated platelets that are efficient at binding to the endothelial cells and improve the extravasation of the tumor cells into the surrounding tissues. Thus, all together this helps in tumor cell metastasis.[8,9]

Tumor neoangiogenesis and tumor vasculature hemostasis
The α granules in the activated platelets secrete various pro-angiogenic and angiogenic proteins like platelet-derived growth factor, vascular endothelial growth factor and angiopoietin-1 that help in the formation of new vascular channels around the malignant tumor.[10,11] To add to the complication, recent studies suggest that platelets appear to be essential for regulating tumor vasculature hemostasis and for preventing intratumoral hemorrhage. This new effect is independent of the platelets’ capacity to form thrombi and instead depends on their granule secretion.[11]

Guiding the formation of “early metastatic niches”
Platelets help in granulocyte recruitment by the secretion of chemotactic factors for the granulocytes. Granulocytes may further inhibit or promote the tumor growth and metastasis depending on the microenvironmental cues. Studies have shown that specific inhibition of platelet-derived signals or platelet-granulocyte interactions might limit metastatic progression by preventing the formation of the early metastatic niche.[12]

In case of benign tumors, there is no additional secretion of platelet count raising substances like thrombopoietic cytokines and platelets that are present preoperatively are the ones that are formed due to the normal physiological secretions of cytokines. After surgery, there is no reduction in these platelet-producing substances. Rather a phenomenon of wound healing that takes place after any other surgery renders a rise in the platelet levels postoperatively.[12]

Clinical implications
Prognostic implications
In patients with malignant neoplasms, the postoperative platelet count should seem to fall down the previous levels. No change or a rise in it can be suggestive of some residual malignant cells and a threatened prognosis. Furthermore, flow cytometry, fluorescence microscopy and intravital microscopy can detect the TCIPA in the circulating blood and indicate the higher possibility of discovering metastasis.

Therapeutic implications
Various sites in the platelet-tumor interaction can be targeted to reduce metastasis. The biggest progress has so far been made in the field of P-selectin inhibition by unfractionated heparin or certain low molecular weight heparins.[8] This would inhibit the binding of platelets to tumor cells and further formation of TCIPAs that help in metastasis. Other receptors such as GPIb-IX-V, GPVI and Integrin α2β1 may also be targeted for the same; however, further research and clinical trials are demanded.

CONCLUSION
Platelets have a catastrophic role to play in cancer biology. The study substantiates the research data available on the mechanism of tumor cell-platelet crosstalk by corroborating a raised level of platelets in the blood in the presence of malignancy and a fall after the elimination of it. Thus, with a firmer insight of this disastrous role of platelets in cancer patients, appropriate drugs can be formulated that can act as adjunctive cancer therapy without negotiating the beneficial role of platelets.

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Conflicts of interest
There are no conflicts of interest.

\[<0.0001\]
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