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EDITORIAL

Immune signature of small bowel adenocarcinoma and the role of tumor microenvironment

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Abstract

In this editorial we comment on the article published "Clinical significance of programmed cell death-ligand expression in small bowel adenocarcinoma is determined by the tumor microenvironment". Small bowel adenocarcinoma (SBA) is a rare gastrointestinal neoplasm and despite the small intestine's significant surface area, SBA accounts for less than 3% of such tumors. Early detection is challenging and the reason arises from its asymptomatic nature, often leading to late-stage discovery and poor prognosis. Treatment involves platinum-based chemotherapy with a 5-fluorouracil combination, but the lack of effective chemotherapy contributes to a generally poor prognosis. SBAs are linked to genetic disorders and risk factors, including chronic inflammatory conditions. The unique characteristics of the small bowel, such as rapid cell renewal and an active immune system, contributes to the rarity of these tumors as well as the high intratumoral infiltration of immune cells is associated with a favorable prognosis. Programmed cell death-ligand 1 (PD-L1) expression varies across different cancers, with potential discrepancies in its prognostic value. Microsatellite instability (MSI) in SBA is associated with a high tumor mutational burden, affecting the prognosis and response to immunotherapy. The presence of PD-L1 and programmed cell death 1, along with tumor-infiltrating lymphocytes, plays a crucial role in the complex microenvironment of SBA and contributes to a more favorable prognosis, especially in the context of high MSI tumors. Stromal tumor-infiltrating lymphocytes are identified as independent prognostic indicators and the association between MSI status and a favorable prognosis, emphasizes the importance of evaluating the immune status of tumors for treatment decisions.

Key Words: Programmed cell death 1; Programmed cell death-ligand 1; Programmed death ligand; Small bowel adenocarcinoma; Tumor infiltrating lymphocytes; Tumor microenvironment; Microsatellite instability

Core Tip: Small bowel adenocarcinoma (SBA) is an uncommon gastrointestinal tumor, accounting for fewer than 3% of all cases, even though it constitutes 95% of the gastrointestinal tract. SBA, which is mostly located in the duodenum, typically goes undetected for a long period of time, resulting to a late-stage discovery and a dismal prognosis. The immunological response, consisting of CD4+ and CD8+ T-lymphocytes, is critical in determining the prognosis. Programmed cell death 1/programmed cell death-ligand 1 (PD-L1) pathway, which is known to be involved in immune evasion in cancer, is implicated in SBA, with PD-L1 expression to a variety of prognostic consequences. The complicated interaction of immunological components, including as TILs and regulatory T cells, emphasizes the complexities of SBA.

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INTRODUCTION

Small bowel adenocarcinoma (SBA) is an uncommon condition, accounting for less than 3% of all gastrointestinal neoplasms. Its rarity comes in contrast with the facts that small intestine constitutes 95% of the surface area of the entire gastrointestinal tract. Adenocarcinomas, constituting around 40% of malignant small bowel tumors, predominantly manifest in the duodenum, with a notable prevalence of 50%–55%[1-4]. SBA presents a challenge in terms of early detection, as it is frequently asymptomatic for an extended period (2 to 8 months), leading to late-stage discovery and poor prognosis. Its detection often arises from complications such as intestinal perforation, ileus, and unbridled gastrointestinal hemorrhaging and by the time of the diagnosis, nearly one-third of individuals are presented with distant metastasis and an advances stage[1,2,5-7]. However, the advanced stage of the diagnosis and the lack of effective chemotherapy lead to a poor prognosis. In terms of treatment options, platinum-based combination chemotherapy with 5-fluorouracil is commonly used and mostly palliatively, and five-year overall survival (OS) rate reaches as high as 30% for locally advanced tumors[3,8].

Malignant small bowel tumors, are often associated with genetic disorders such as familial adenomatous polyposis, Lynch syndrome, Peutz–Jeghers syndrome, and juvenile polyposis, or risk factors including chronic inflammatory conditions like Crohn's disease and coeliac disease, along with environmental factors like smoking, alcohol, and certain dietary habits[2,9-11]. The tumorigenesis of SBAs is believed to align with colorectal cancer (CRC), although chronic inflammation may lead to a distinct sequence of inflammation–dysplasia–adenocarcinoma in some cases[2,12]. The small bowel's unique characteristics, including rapid epithelial cell renewal, preventing the accumulation of genetic damage, an active immune surveillance as it is the largest organ of the immune system, contribute to the rarity of these tumors. High intratumoral infiltration of CD3+ and CD8+ cytotoxic T-lymphocytes, along with the presence of tertiary lymphoid structures, is associated with a favorable prognosis[1,2]. Moreover, microsatellite instability (MSI) in SBA, varies between 5% and 35%, exhibiting a high tumor mutational burden, potentially contributing to the unique characteristics of these cancers[2,3,9].

Evading immune surveillance through the Programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway is a hallmark of cancer. PD-L1, a key player in modulating the tumor microenvironment (TME), is upregulated in various solid tumors, including gastrointestinal cancers[1,2]. Studies have shown the efficacy of blocking the PD-1/PD-L1 signaling pathway in gastrointestinal cancers with high MSI (MSI-H), establishing a significant association between MSI-H and PD-L1 expression in SBA[1]. Interestingly, the relationship between PD-L1 expression and prognosis in gastric and CRC remains contentious. While some studies suggest a favorable prognosis associated with PD-L1 expression, others indicate a poorer prognosis in these cancers, with the effectiveness of anti-PD-L1/PD-1 therapy relying on tumor-infiltrating lymphocytes (TILs), mainly composed of CD8+ T cells[1,2]. The abundance of TILs has been linked to improved survival, emphasizing the crucial role of the immune system in combating small bowel cancers[2]. However, the presence of regulatory T cells, characterized by the expression of FoxP3, within TILs introduces an immunosuppressive element, potentially hindering the efficacy of therapy. A high ratio of FoxP3+ to CD8+ T cells is correlated with poor clinical outcomes in digestive system cancers[1]. In this Editorial we elaborate on the TME, the infiltration of immune cells and the immune status of the tumor, stromal and immune cells.

THE ROLE OF PD-1, PD-L1 AND TILS IN SMALL BOWEL ADENOCARCINOMA

PD-1 is an immunoinhibitory receptor expressed on the surface of CD4+ and CD8+ T cells, B cells, natural killer cells, and monocytes. Its binding to PD-L1 Leads to the inhibition of immune suppression in these cells. Tumors expressing PD-L1 are considered immune-active, generating an immunosuppressive microenvironment. Consequently, PD-L1-positive tumors may be associated with a poor prognosis[1,13].

Given that the PD-1/PD-L1 pathway provides a potential immune escape route for tumors, an increase in PD-L1 expression is anticipated in advanced disease. Although PD-1/PD-L1 expression is expected to suppress the immune reaction against tumors, reports on the prognostic value of PD-L1 expression vary across different cancer types[2,3]. PD-

L1 expression has been shown to correlate with a poor prognosis in esophageal cancer, pancreatic carcinoma, hepatocellular carcinoma, renal cell carcinoma, and ovarian cancer. However, in breast cancer and Merkel cell carcinoma, PD-L1 has been found to correlate with a better patient outcome. For lung cancer, melanoma, gastric cancer, and CRC, both positive and negative prediction values have been reported[2,13,14]. One potential reason for this discrepancy in results may be attributed to the wide variation in the definition of PD-L1 positivity, with the cutoff for positive staining ranging from 1% to 50%. Nevertheless, the mere existence of PD-1/PD-L1 factors allows for the possibility of utilizing targeted immunotherapy in the context of precision medicine.

Microsatellite unstable tumors are characterized by an extensive mutational load, resulting in truncating mutations identified by immune surveillance due to misfolded proteins serving as neoantigens[2,15,16]. This leads to an enhanced antitumoral immune reaction and, consequently, improved survival. MSI status is linked to a high number of PD-1 positive immune cells and PD-L1 expression in immune cells[2,3].

PD-L1 can be expressed by tumor cells (PD-L1TC) or peritumoral inflammatory cells, predominantly histiocytes. PD-L1 expression in tumor cells ranges from 25% to 43%, while in tumor-infiltrating immune cells, it can reach as high as 54% [1,3,9,13]. PD-L1 expression is also increased in MSI tumors (86%) compared to those with microsatellite stable (MSS, 21%). Furthermore, PD-L1 expression is associated with the underlying cause of the tumor. Giuffrida *et al*[17] observed that when SBA is associated with coeliac disease or Crohn's disease, the expression is around 35%, while in sporadic cases of SBA, the expression is only 5%. Increased PD-L1TC is associated with a deeper depth of invasion ($P < 0.005$), increased infiltration of T-lymphocytes (CD3+, CD4+, and CD8+), and a 5-year OS of 74%, compared with PD-L1 negative SBAs[1,3,13]. The appearance of PD-L1 in tumor-infiltrating immune cells leads to a better prognosis, reducing the probability of peritoneal metastasis ($P < 0.05$), increasing the 5-year Disease-Specific Survival to 81%, compared to 33%, and the OS to 74% *vs* 27% in PD-L1 negative cases[2]. Thota *et al*[3] observed that 72% of patients with PD-L1 expression in immune cells had necrosis in the invasion border[3]. Moreover, Klose *et al*[13] support that the absence of PD-L1 in SBAs is correlated with female gender, increased tumor recurrence, metastasis, higher staging, and higher rates of postoperative administration of chemotherapy[13].

PD-1 expression is also increased in SBAs, especially in MSI-H tumors. According to Wirta *et al*[2] and Thota *et al*[3], all MSI-H tumors showed increased expression of PD-1, whereas only 75% of MSS tumors did[2,3]. This is directly related to a smaller tumor-node-metastasis (TNM) staging, with only 9% of patients in stage IV and 42% reported to have stage I or II, positively affecting the OS of the patients[2,9]. However, MSI is present in around 32% of SBA patients, and MSI-H varies from 10% to 21.7%, altering the appearance of PD-1, as MSI, in general, is related to PD-1 expression only in 37.5% of cases[13,18,19]. The 5-year OS in patients with MSI is 60%, while in patients with MSS, it is 54%. Pedersen *et al*[19] in the second phase of their multicenter study, using Pembrolizumab in patients with advanced SBA, observed that 2 patients with MSI-H had a confirmed partial response (50%), while only one (3%) from the MSS/MSI-Low group had a confirmed partial response, and 1 had an unconfirmed response. The responders had an average duration of response of 28.5 months in the MSI-H group and 17.5% in the MSS/MSI-Low group[19]. MSI status, along with PD-1 and PD-L1 expression, may be a helpful predictor for the prognosis of patients and for treatment selection.

TILs play a crucial role in the complex microenvironment of SBA. These specialized immune cells are found within the tumor tissue and are integral components of the host's anti-tumor response. In SBA, the presence and activity of TILs are of particular interest, as they are implicated in both the progression and potential control of the disease. In particular, the appearance of CD8+ TILs in the tumor or the stroma is correlated with less lymph node (LN) metastasis, fewer distant metastases, less peritoneal seeding, and an earlier TNM stage ($P < 0.005$)[1]. Increased percentages of TILs are also correlated with the infiltration of B cells, dendritic cells, and natural killer cells, enhancing the immune response. Along those lines, T-reg and T-helper cells might also be present, regulating the immune response and leading to a worse prognosis[5,20,21]. FoxP3 T-reg cells are associated with deeper depth of invasion, but this association is not significant. However, the increased ratio of FoxP3 to CD8+ cells is significantly associated with a worse prognosis, peritoneal, LN, and distant metastasis ($P < 0.005$)[1]. Moreover, low percentages of CD8+ cells lead to peritoneal seeding ($P = 0.003$), worsening the prognosis[9]. Parkes *et al*[14] observed that infiltration of CD3+, CD4+, and CD8+ T-cells leads to a better progression-free survival rate ($P < 0.005$), and CD8+ cells are also associated with increased OS, although the *P*-value was more than 0.05[14]. According to the multicenter cohort of Noh *et al*[9], the best prognosis was observed in patients with high PD-L1 and high CD8+ TILs in SBA[9].

CONCLUSION

The presence of PD-L1 and PD-1 in SBAs, in contrast to other cancer types, contributes to a more favorable prognosis. Patients with SBA and MSI-H tumors exhibit superior OS rates compared to those with MSS tumors. Similarly, individuals with elevated stromal tumor-infiltrating lymphocyte (sTIL) levels in SBA demonstrate extended OS times, establishing sTIL as a robust independent prognostic indicator. Furthermore, MSI status is closely associated with a favorable prognosis, particularly in the context of MSI-H tumors, and is directly correlated with PD-1 expression. The calculation of a Combined Positive Score is pivotal for evaluating the immune status of tumors and establishing a pertinent cut-off value for the treatment of patients with anti-PD-1/PD-L1 factors.

FOOTNOTES

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