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REVIEW ARTICLE

Immune tumor board: integral part in the multidisciplinary management of cancer patients treated with cancer immunotherapy

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Abstract

Recent progress in the understanding of immune responses to cancer and how tumor cells evade immune control have led to the successful introduction of cancer immunotherapy, in particular immune checkpoint inhibitors (ICI). Treatment of cancer patients with immunotherapy such as ICIs has led to new challenges, including starting and stopping rules for immunotherapy, the management of immune-related adverse events, and logistic issues for the production of cellular therapies and viral delivery vectors. These challenges are not disease- or organ-specific and several potential biomarkers to predict response to ICI are under investigation. We installed an interdisciplinary discussion platform for managing patient-specific challenges associated with cancer immunotherapy in our institution. Here, we describe an immune tumor board for the management of cancer patients treated with immunotherapy and provide an outlook on how such a platform could be potentially used in the future to discuss rational and personalized combination therapies, and how to improve the management of side effects occurring under immunotherapy.

Keywords Immune checkpoint inhibitors · Immune-related adverse events · PD-1 · CTLA-4 · Cellular therapies

Introduction

The mammalian immune system can recognize aberrantly expressed or altered proteins from mutated genes produced by malignant cells which can nowadays be used clinically to efficiently eliminate developing cancers [54, 56]. During cancer progression, tumor cells are not only able to overcome intrinsic cellular control mechanisms, but also evade external control through the immune system [42, 49, 57]. Tumor cells generate a strongly immunosuppressive tumor microenvironment that includes the upregulation of inhibitory receptors on effector immune cells such as $CD8^+$ cytotoxic T cells [42]. Such immune evasion by tumor cells is essential for cancer progression and, therefore, recognized as a hallmark of cancer [19]. Understanding of the mechanisms that lead to cancer immune evasion and immune suppression has led to the generation of new drugs for cancer immunotherapy. For example, reversal of cancer-associated immune suppression by targeting inhibitory receptors (immune checkpoint inhibitors, ICI) can lead to remissions and long-term control of cancer even in patients at advanced stages [49, 58, 66]. Antibodies that block immune inhibitory pathways such as the CTLA-4 receptor or PD-(L)1 pathway are approved for the treatment of many tumor types including melanoma, non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma (RCC), head and neck cancers, bladder cancer, and mismatch repair deficient intestinal cancers including colorectal cancer [66]. This novel class of therapeutics has provided clear evidence that immunotherapy can restore anti-cancer immunity to mediate efficient tumor control and can therefore be successfully applied to a broad spectrum of cancers.

Strikingly, in some responding patients, long-term remission is observed. For example, in patients with metastatic melanoma treated with the CTLA-4 inhibitor ipilimumab, an

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approximate 20% survival rate was observed after 10 years [55]. Even greater long-term responses are seen in a larger percentage of patients treated with PD-(L)1-targeted monotherapy or combination therapy with CTLA-4 and PD-(L)1 inhibitor [70].

Several other immunotherapeutic approaches are also being developed. Classes of immunotherapies can be divided into targeted approaches, such as vaccinations with defined tumor-specific antigens including neoantigens [54, 56], targeted therapy with genetically modified T or natural killer (NK) cells including cells transduced with tumor-specific T cell receptors (recombinant TCR), or chimeric antigen receptors (CARs)–chimeric constructs of antibodies and intracellular domains that can stimulate T or NK cells (CAR T or CAR NK cells) [28, 52]. Conversely, untargeted approaches, such as general stimulation of the immune system with ICIs or cytokines and targeting of activating receptors, are also quite successful [66]. In addition, ex vivo stimulation and expansion of tumor-infiltrating lymphocytes (TILs) with cytokines and autologous retransfusion can be used as active immunotherapy (TIL transfer) [28, 43, 52]. Current approaches are mainly based on combination immunotherapies to enhance the efficacy of single agents [38, 44, 71]. Also, combination of classical chemotherapy and targeted small molecules with checkpoint inhibitors show promising results [7, 38, 44, 71].

While immunotherapy has emerged as new treatment paradigm across a broad spectrum of malignancies, these therapies are associated with a unique spectrum of inflammatory side effects termed immune-related adverse events (irAEs) [29, 34]. Their management requires prompt recognition and treatment as various organ systems, including the skin, gastrointestinal tract, endocrine organs, and lung, can be affected [18, 34, 41, 47, 48]. Severe grade 3–4 irAEs are found in approximately 22–24% of patients with the CTLA-4 inhibitor ipilimumab and in approximately 10% with PD-(L)1 blocking antibodies [18, 47, 48].

To provide multidisciplinary care for cancer patients treated with immunotherapy, we installed a biweekly tumor board for cancer immunotherapy in 2016 at the University Hospital in Basel, Switzerland. Here, we will discuss the current and potential future status of a tumor board for cancer immunotherapy.

Why do we need a tumor board for cancer immunotherapy?

Current and future challenges of cancer immunotherapy

Organ-specific tumor boards cover the interdisciplinary management of a certain cancer type. In contrast, tumor boards such as molecular boards or boards for cancer immunotherapy focus on clinically relevant questions on patient management, irrespective of the origin of the tumor. In molecular tumor boards, genetic and epigenetic alterations that can be targeted with drugs are the focus. In our tumor board for cancer immunotherapy, patients are discussed to define the relevance of prognostic/predictive biomarkers, to identify treatment strategies including sequencing and combinations, and to manage irAEs. These are discussions that incorporate clinical data, radiology reports, classical morphological analysis, as well as molecular analysis of the tumor tissue; thus, oncologists, pathologists, radio-oncologists, hematologists, clinical immunologist, radiologists, and specialists of different disciplines from internal medicine (e.g., endocrinologist, gastroenterologist etc.) as well as molecular biologists and immunologists are involved. The audience of such a board is distinct from other organ-focused boards and has specific expertise, which helps to significantly improve the management of patients undergoing immunotherapy. Following a short presentation of the patient's history, an interdisciplinary team of medical oncologists, pathologists, radio-oncologists, and specialists such as gastroenterologists, neurologists, or endocrinologists discuss the case and are responsible for the interdisciplinary management of the patients. Such tumor board could also act as a gatekeeper to support the rationale use of cancer immunotherapies.

The rapid evolution of new immunotherapeutic options and associated irAEs introduces several challenges for the treatment of cancer patients with immunotherapy. Current approaches, including treatment with ICIs, require a good network of specialists that are familiar with the drugs and their side effects. Thus, our immunotherapy board primarily focuses on the management of irAEs and also on the indication for immunotherapy in patients in which immunotherapy is not yet a standard therapeutic option.

Management of irAEs

Optimal treatment of irAEs is an important aspect of patient management and a central aspect of the multidisciplinary discussion. In principle, all organ systems can be affected by the inflammation induced by immunotherapy. While several recent reviews have summarized common and less common side effects and provided treatment recommendations for irAEs [18, 47, 48], most of these guidelines provide only general guidance of the treatment of different organ toxicities. Yet, the timing, dynamics, and severity of clinical symptoms vary largely and need to be considered in individual clinical decision-making. For example, skin toxicity can present as either an acute maculo-papular rash with acute inflammation or as slowly appearing psoriasiformic dermatoses, both of which require a different management approach. In general, patients with slowly appearing psoariasiformic skin toxicity can continue ICI therapy and only require local therapy. Conversely, grade 3–4 acute skin toxicity requires quick

administration of high-dose corticosteroids and interruption of ICI therapy in most cases. Individual treatment plans are often discussed at the immunotherapy boards in the event of a severe or rare irAEs. Discussion includes patients with irAEs that do not respond to standard immune suppression with corticosteroids (steroid-resistant), those who develop a dependency on corticosteroids (steroid-dependent), or patients with resistance to additional immunotherapeutics such as mycophenolate mofetil (MMF). The multidisciplinary team will decide whether or not biopsies should be performed in the aforementioned clinical situations.

A special focus of the immunotherapy board is rare toxicities. Our board was among the first to report cardiac toxicity in a patient undergoing PD-1 blockade for metastatic melanoma [32]. In this instance, the severe cardiac dysfunction and arrhythmia could be controlled by corticosteroids and heart insufficiency therapy [32]. Others have since reported similar cardiac toxicity [25]. We have also reported cases of generalized inflammation [30] and encephalitis due to microvascular cerebral vasculitis with anti-endothelial antibodies [33]. All those cases have been intensively discussed during the tumor board.

Personalized approaches in cancer immunotherapy

One major challenge in cancer immunotherapy is the identification of the right patient for the right therapy. An important step for decision-making will be the development of biomarkers to predict response to ICI (see below) [71]. While PD-(L)1 mono-blockade is often well tolerated, many trials have included only patients with good performance status (PS, initially an Eastern Cooperative Oncology Group [ECOG] PS of < 2). Patients with poorer PS (ECOG PS 2 or 3) are discussed by the interdisciplinary team, in particular in the light of combination therapies. Currently, ICIs are approved that target CTLA-4 or PD-(L)1. Combination therapies with CTLA-4 and PD-(L)1-blocking antibodies are already approved or will soon be approved for several cancer types [46, 70, 71]. Multiple trials are ongoing that combine different immunotherapies, and also with targeted therapy and chemotherapy. While these approved drugs cover only some approaches, it is conceivable that in the next 3–5 years, several new therapeutic approaches will be available and the complexity of treatment decisions and management of side effects will increase further [7]. In addition to treatment and clinical decision-making, new treatment modalities, including cellular therapies such as preparation of TILs or CAR T cells, are currently being developed [52]. Other logistic challenges include the application of viral vectors for vaccination and oncolytic viruses for immune stimulation. Having additional therapeutic options will certainly benefit many additional patients, but the question of the right sequence with regard to other anti-neoplastic therapies adds to the complexity of optimal management in these patients.

Patients with co-morbidities, in particular auto-immune disorders, should be managed by an interdisciplinary team. Several reports exist of patients treated with ICIs that have chronic auto-immune disorders [9, 27]. The incidence of severe irAEs is increased in patients with pre-existing autoimmunity [9, 27]. In one study, 44% of patients had an irAE [9]. Even patients after allogeneic hematopoietic stem cell transplantation with a high chance of inflammatory complication had been treated with ipilimumab successfully [11]. In melanoma patients, irAEs with previous ICI therapy must be considered, since they increase the risk for a secondary irAE with subsequent immunotherapy [17, 22, 39]. Flares can be often observed in patients treated with PD-1-targeted antibodies when irAEs were observed during previous ipilimumab therapy [17, 22, 39]. Nevertheless, patients with previous irAEs during CTLA-4 blockade can be successfully treated with PD-1-blocking antibodies when patients are followed by immunotherapy-experienced physicians [17, 22, 39].

An ongoing issue in patients treated with ICIs is the duration of therapy. In some trials, patients with NSCLC were treated with PD-(L)1 inhibitors until progression or toxicity that prompted the cessation of the drug [4, 5, 13]. In other trials, ICIs were stopped after 2 years [21]. Thus, the exact duration needed remains unclear. Recently, results from the CheckMate-153 study were presented at the European Society for Medical Oncology annual meeting 2017 [62]. A fixed duration of 1-year's treatment with nivolumab versus treatment until progression or toxicity was tested in patients who had already benefited from treatment with nivolumab at least for 1 year before randomization. Although the group with continuous therapy had a superior outcome, the groups were biased, and one should be cautious to draw final conclusions from the presented data. Further studies are urgently needed that define stopping rules in patients achieving long-term responses. Currently, management needs to be adapted to the clinical situation which is best defined in an interdisciplinary team.

What is the role of the pathologist in the immunotherapy board?

Immunohistochemical and molecular analysis of tumor tissue samples to predict the outcome of a planned immunotherapy, and also in the future to predict rational combination therapy, are key contributions of pathologists to improve our treatment algorithms. In addition to classical analysis, also NGS-based expression analysis of inflammatory markers/immune-related genes and also FACS analysis as well as liquid biopsies will help for decision-making. Moreover, in cases of ambiguous clinical presentation during immunotherapy with a differential

diagnosis of irAE, histological examination of affected tissues (e.g., gastrointestinal-tract or liver biopsies) can help achieve a final diagnosis.

Biomarkers for immune checkpoint inhibitors

Understanding the biological mechanisms of primary and secondary resistance to immunotherapy will help to develop biomarkers to predict treatment responses and also to define patients that need combination therapy versus patients that can be treated with monotherapy. Different mechanisms of resistance to PD-(L)1 blockade have been described, including defects in human leukocyte antigen (HLA) class I presentation, adaptation of the tumor microenvironment, low mutational burden, and mutations or defects in the interferon-γ(IFNγ) pathway [2, 8, 20, 45, 59]. Two studies have identified mutation downstream of IFNγ signaling in janus kinase-1 (JAK1) or JAK2 as mediators of primary or secondary resistance in patients with malignant melanoma [2, 59]. Several oncogenic pathways have also been linked to resistance to checkpoint blockade and even the microbiome has been associated with mediating resistance to ICIs [45]. The concept of "hot, excluded and cold" tumors has been discussed in the recent literature [7]. "Hot or inflamed" tumors have infiltrating, tumor-specific (most often neoantigen-recognizing) T cells within the tumor. The immune system is evaded by adaptive immune suppressive mechanisms including upregulation of PD-L1 or local immune suppression by regulatory T cells or myeloid cells. "Excluded" tumors are immunogenic and, therefore, tumors are recognized by immune cells, but tumors cannot be efficiently invaded by anti-tumoral immune cells. Finally, "cold" tumors are immune deserts with very low level immune responses to the cancer. Studies to define standardized methods to classify tumors accordingly are ongoing.

Several potential biomarkers to predict the response to ICI therapy have been identified and studied (Table 1). While the presence or absence of ligands for immune checkpoint such as PD-ligand 1 or 2 (PD-L1/2) is currently being investigated, recent analyses have also focused on molecular alterations, including immune signatures and neoantigen formation [7, 71]. In addition, the characterization of T cell dysfunction and the presence of anti-tumoral T cells might potentially serve as predictive biomarkers for cancer immunotherapy [65]. For example, recent immunohistochemical analyses supported by digital pathology have suggested that the presence of anti-tumoral T cells in NSCLC predict the response to ICI therapy. Biomarkers could also serve as predictors for rationale combination therapies [7, 71]. Several studies have shown that inflamed or "hot" tumors respond better to ICI therapies [7]. Hot tumors can be differentiated from cold tumors by immunohistochemistry or by measuring RNA expression of inflammatory markers. Differentiation of excluded tumors is mainly possible through immunohistochemistry. Patients with non-inflamed tumors (excluded or cold) should probably be treated with combination therapies [7, 71]. Excluded tumors could be potentially treated with combinations of anti-angiogenic agents for vessel normalization and PD-(L)1 inhibitors [68]. Cold, non-immunogenic tumors have to be rendered immunogenic and combination of ICI therapy with vaccinations or radiotherapy can be considered [7, 71]. While immunohistochemical staining for PD-L1 and tumor-infiltrating leukocytes can help for decision-making, potential new biomarkers will be introduced in the near future and will help to choose the right immunontherapy for the right patient. Expression analysis of inflammatory markers and immune-related genes have been associated with the response to ICI therapy [24, 40, 61] and NGS-based expression analysis could help to distinguish between hot and cold tumors. Also, FACS-based analysis of peripheral or tumor T cells could potentially support decision-making. For example, recent analysis has shown that higher levels of Ki67 or PD-1 in $CD8^+$ T cells are associated with the response to the ICI therapy [23] Thommen, 2018. In melanoma patients responding to CTLA-4-blocking antibodies, $ICOS^+$ $CD4^+$ tumor-infiltrating T cells were found by multiplex mass cytometry (CyTOF) to be associated with a favorable response [69]. Thus, FACS analysis of $ICOS^+$ $CD4^+$ T cells could be potentially used, although protocols for preparation of cell suspensions from tumors require quite large samples.

Tumor mutational burden (TMB) as a proxy for tumor foreignness is an important marker for immunogenicity and also response to ICI therapy [20, 56]. Melanoma patients with a higher mutational burden have an improved response to CTLA-4-blocking therapy [60]. Similarly, NSCLC patients with higher mutational burden show an improved outcome when treated with PD-1 inhibitors [50]. The FDA has approved PD-(L)1 blockade in patients with MMR deficient or MSI high tumors, irrespective from where the tumors originate, since they have a high mutational burden. This will have a substantial impact on the diagnostic workload of pathology departments. A recent study suggests that structural changes including insertion-deletion-associated changes are more immunogenic than single nucleotide changes [67]. Another factor is subclonal mutations. In addition, mutations that are only present in a fraction of tumor cell clones are associated with a higher chance of resistance to ICI than mutations/potential neoantigens that are present in the majority of tumor cell clones [36].

Potential biomarkers for the prediction of irAEs

Biomarkers for irAEs would be helpful to spare patients from severe toxicities. The underlying pathologic mechanisms associated with irAEs after checkpoint blockade and the

Table 1 Potential biomarkers for immune checkpoint inhibitors in cancer

Biomarker	Association	Literature
PD-L1	High expression associated with better outcome	[6, 14, 37]
TMB	High TMB associated with better outcome of ICI therapy	[20, 35, 50, 60]
Immune contexture	Infiltrating immune cells, inhibitory and activating immune cells are associated with outcome	[8, 10, 51, 61, 69]
IFNγsignature, mutations in JAK1/2 signaling	IFNγsignature is associated with better outcome, mutations in the pathway associated with primary and secondary resistance	[2, 3, 15, 26, 59, 72]
T cell dysfunction, presence of anti-tumoral T cells	High frequency of PD-1 tumor T cells associated with better outcome	[65]
Peripheral, circulating cells	High level of monocytes associated with worse outcome, Ki67+ T cells in peripheral blood associated with better outcome of PD-1 blockade	[12, 23, 31, 63, 64]
Microbiome	Certain bacteria associated with improved outcome, anti-microbial treatment associated with worse outcome	[16, 45, 53]

breakdown of tolerance towards self-antigens in patients with irAEs are not completely understood [29]. Preclinical models and correlative human studies have provided first insights. The physiological role of the PD-1/PD-L1 pathway is to mediate peripheral tolerance of T cells and inhibition; immune checkpoints could break such tolerance [29]. Identification of T cell clones by sequencing of the complementarity-determining regions 3 (CDR3) of the TCR beta chain detected similar clones in auto-immune lesions in cases of myocarditis and pneumonitis [1, 25]. These findings support a hypothesis that shared antigens in the tumor and the irAE-affected organ can lead to auto-immune disorders by cross-presentation of such shared antigens [29]. Another potential mechanism is the exacerbation of previously subclinical auto-immune syndromes [33]. We have previously described a case in which anti-endothelial antibodies were already present before the initiation of PD-1 blockade and upon treatment, the patient developed a cerebral vasculitis with necrosis of brain tissue [34]. An additional postulated mechanism of irAE induction is via epitope spreading during checkpoint blockade [29]. In general, however, currently there is no clear biomarker for the prediction of toxicity available and additional mechanistic studies and clinical evaluations are needed.

Case studies: the role of the tumor board

The immune tumor board integrates all disciplines involved in the diagnosis and management of patients undergoing cancer immunotherapy. The tumor board is a part of broader network for cancer immunotherapy at the University Hospital Basel, which consists of a clinical part (trials, tumor board, patient management, set up of TIL transfers) and a translational part (Laboratory for Cancer Immunotherapy, research groups at the Department of Biomedicine). Reporting is not yet standardized on evidence levels but rather a consensus statement is given. We present two cases that illustrate the discussions and clinical utility of our tumor board for cancer immunotherapy.

Case 1—defining the treatment indication for cancer immunotherapy

This first patient is a 32-year-old male with an alveolar soft part sarcoma (ASPS) on his right lateral calf and multiple lung and cerebral metastases. After whole brain radiotherapy and local radiotherapy of the primary tumor, the patient was treated initially with a doxorubicin-containing regimen that also included bevacizumab. Following partial remission, subsequent bevacizumab maintenance therapy was initiated. Yet, stereotactic irradiation was needed twice to control single metastases in the right tibia plateau and lung. In addition, one right frontal large brain metastasis became symptomatic and was removed surgically. After 2 years, the patient had a systemic progression and therapy was changed to pazopanib with a best response of stable disease. A short course of sunitinib was tried without success. A new biopsy of a soft tissue lesion on the back of the right foot was performed and an analysis for targetable mutations was done (Oncomine Comprehensive Panel, ThermoFisher). No alterations were detected. Immunohistochemistry, however, revealed a strong expression of PD-L1 (Fig. 1a, b) in nearly all tumor cells. We discussed the case and the evidence in our tumor board

and decided to initiate a treatment with pembrolizumab. Before the start of immunotherapy, the patient had multiple soft tissue metastasis, lung metastasis, and cerebral metastasis (Fig. 1c). After 3 months, the lesions were stabilized. After 6 months, we observed a partial remission (Fig. 1c). The patient currently has no adverse events and a very good quality of life 5 years after the diagnosis of his advanced soft tissue sarcoma. We are continuing the treatment for at least 2 years.

Case 2—defining the interdisciplinary management of irAEs

A 36-year-old male melanoma patient was repeatedly discussed at our tumor board for cancer immunotherapy. The patient had previously had an intestinal mass removed surgically at a regional hospital. Histological examination showed a BRAF V600E-mutated melanoma and an ^{18}FDG-PET/CT scan revealed affected retroperitoneal lymph nodes. The patient had known ankylosing spondylitis (Bechterew disease), but currently no activity of his autoimmune disorder. He had a history of infliximab treatment and had experienced a serious anaphylactic reaction to infliximab injection. Treatment with anti-PD-1 and anti-CTLA-4 combination immunotherapy was initiated. Within 2 days of the first injection, the patient reported some diarrhea (grade 1). Stool cultures showed no microbiological causality and he was treated symptomatically. Two days later, he returned with an increase in stool frequency. A CT scan of the abdomen showed a thickening of the small intestinal wall. The sigmoidoscopy showed only little changes in the colon and the rectum and the biopsy revealed slight inflammation. With a stool frequency of more than seven per day, we initiated an intravenous treatment with

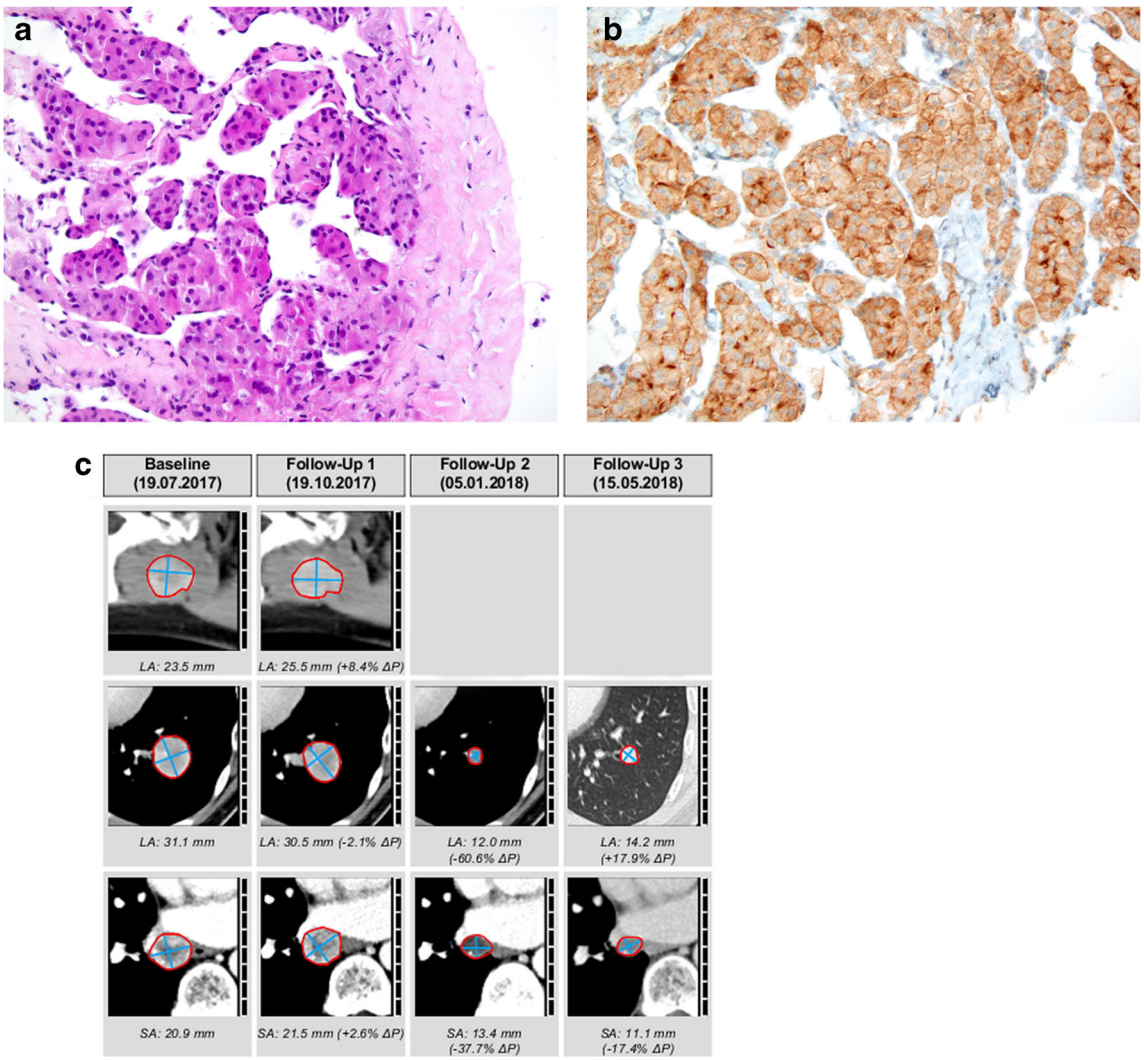

Fig. 1 Case 1. Indication for immunotherapy. **a** Core needle biopsy of a soft tissue lesion on the right foot demonstrating the typical growth pattern of alveolar soft part sarcoma (H&E-stain, 200X). **b** PDL1-immunostain shows a strong expression in virtually all tumor cells (200X). **c** Target lesions were all regressing after PD-1 blockade was started

2 mg/kg prednisone. The symptoms improved, and the patient was discharged after 5 days. However, abdominal discomfort and diarrhea recurred when the steroids were tapered. A CT scan at that time showed increased thickening of the distal small intestinal wall. Corticosteroids were reinitiated and after discussion at our tumor board involving gastroenterologists, we decided to start the integrin-blocking antibody vedolizumab, since the patient had a history of a severe allergic reaction to the TNFα-blocking infliximab. Although diarrhea improved, abdominal pain still persisted and a CT scan of the abdomen showed free air and multiple perforations of the jejunum (Fig. 2a). Emergency surgical removal of the affected intestine showed severe inflammation and transmural infiltration of inflammatory infiltrates (Fig. 2b, c). The patient recovered after surgery and under anti-microbial therapy, but bowel inflammation was ongoing. We discussed the case in our interdisciplinary tumor board and decided to initiate treatment with the fully human TNFα-blocking agent adalimumab. The patient's condition improved over several days and he could be discharged. The anti-cancer treatment was changed to a targeted therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.

Conclusions

In summary, we have presented our concept of an interdisciplinary tumor board for cancer therapy including examples of how treatment decisions are reached. Cancer immunotherapy has benefitted many cancer patients and will continue to improve the prognosis of patients with metastatic and locally advanced cancers. A highly interdisciplinary tumor board to discuss indications for cancer immunotherapy and the right management strategy for side effects has proven to be educational, but more importantly, has significantly impacted clinical decisions such as the choice of immunotherapy or immunosuppressants in patients with corticosteroid-dependent or corticosteroid-resistant irAEs. In the advent of new cancer immunotherapy approaches and emerging combination therapies, the complexity of treatment decisions will increase. Also, the implementation of standardized reporting of board decisions and stating of evidence levels of evidence require additional work. Taken together, interdisciplinary immune tumor boards will become integral and critical platforms for the management of patients treated with cancer immunotherapy.

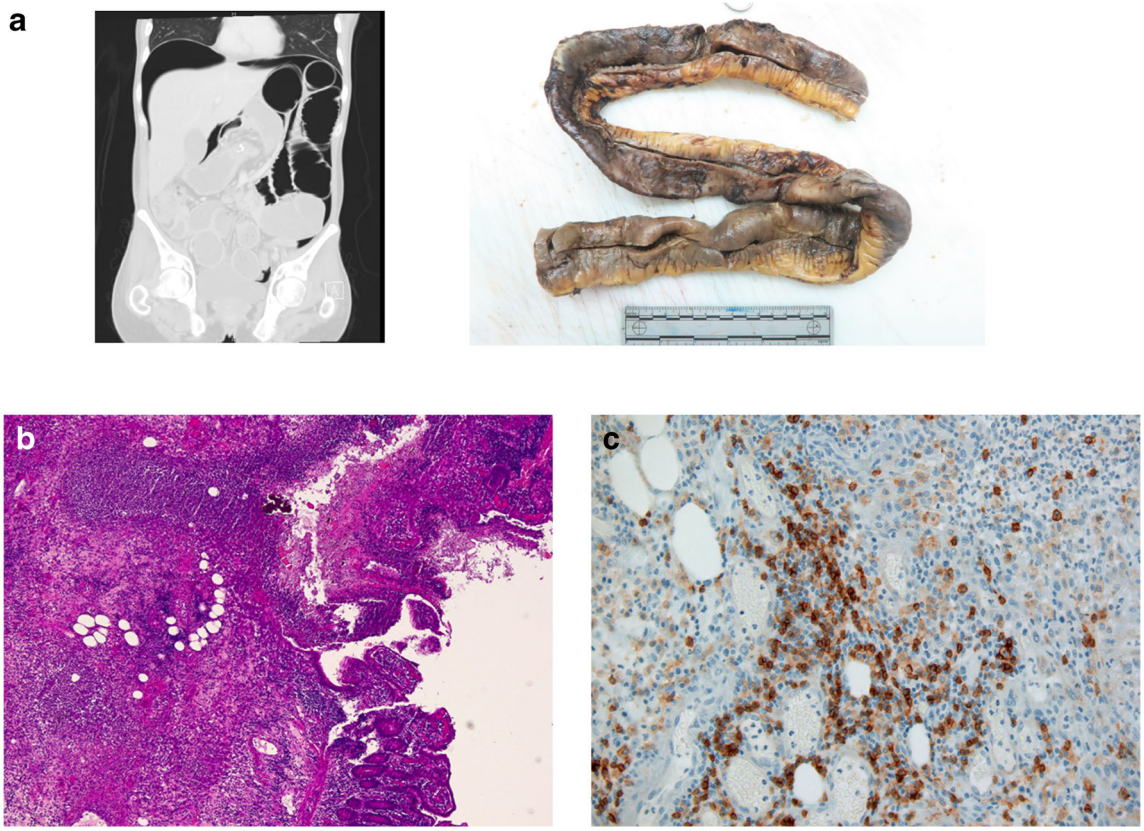

Fig. 2 Case 2. Management of side effects. **a** CT scan and macroscopic image of resected small bowel after perforation. **b** Resection specimen of the small intestine with a deep ulcerating lesion and a transmural inflammatory infiltrate (H&E-stain, 100X). **c** Immunostaining for CD3 highlighting many (activated) T cells at the base of the ulcer (200X)

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Contributions H.L., S.D. and A.Z. wrote the manuscript. H.L. and A.Z. treated the patients that are discussed.

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Compliance with ethical standards

Written informed consent was obtained from the patient for the presentation of the samples and the tissue.

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