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Preoperative testing for immunotherapy-induced endocrinopathy in breast cancer: Real-world data, literature review, and suggested management protocol

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Ethics Committee Approval
This study was a retrospective review of previously collected, anonymized data. In accordance with UK Health Research Authority (HRA) guidance, formal research ethics approval was not required. The research was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the UK General Data Protection Regulation (GDPR).

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Triple-negative breast cancer (TNBC) is an aggressive subtype for which pembrolizumab-based neoadjuvant therapy has demonstrated improved outcomes. However, immune checkpoint inhibitors, including pembrolizumab, are associated with endocrine toxicities such as hypothyroidism, hypophysitis, and adrenal insufficiency, which may significantly complicate perioperative care. This study aimed to evaluate real-world preoperative endocrine testing and propose a practical management protocol.
Methods: This retrospective study evaluated 28 patients with TNBC at Western General Hospital who received pembrolizumab before surgery between March 2023 and December 2024. Clinical data, endocrine function tests, surgical outcomes, and adverse events were analyzed.
Results: Endocrinopathies occurred in a subset of patients, including one case of hypothyroidism and two cases of adrenal insufficiency. Only 36% of patients underwent cortisol testing preoperatively.
Conclusion: We propose a protocol for routine preoperative endocrine screening in this population, including early-morning cortisol and thyroid function tests. Although the incidence is low, these complications may be severe, and implementing this protocol may reduce the risk of perioperative complications associated with immunotherapy-induced endocrinopathies.

Keywords: pembrolizumab, pre-assessment, endocrinopathy, breast cancer

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Introduction

Triple-negative breast cancer (TNBC) is considered an aggressive subtype of breast cancer because of its rapid growth, risk of recurrence, and risk of metastasis. In the United Kingdom, National Institute for Health and Care Excellence (NICE) guidance recommends considering chemotherapy regimens that include the immune checkpoint inhibitor pembrolizumab for high-risk, early-stage or locally advanced TNBC in the neoadjuvant setting. The KEYNOTE-522 trial demonstrated that this approach is associated with improved event-free survival and higher rates of pathological complete response [1-3].

The toxicity and side-effect profile of pembrolizumab is significant and complex. Adverse events of interest reported in the trial literature include endocrinopathies of moderate frequency, including pituitary, thyroid, and adrenal dysfunction [1, 4]. Endocrine deficiencies can occur during immunotherapy or up to six months after its completion and usually persist, requiring lifelong replacement therapy [4, 5].

Primary hypothyroidism is the most common endocrinopathy, occurring in 6%-9% of patients, whereas hyperthyroidism is less common [6]. Immunotherapy-induced hypophysitis occurs in approximately 1% of patients and is often observed later during treatment, with a median onset of six months [6]. Primary adrenal insufficiency is an increasingly recognized adverse event that can present acutely, with a reported incidence of 1%-2% [5, 6]. It has been associated with fatalities resulting from life-threatening adrenal crisis and vasodilatory shock [7]. The onset varies widely from a few days to more than 12 months [6]. In patients undergoing anesthesia and surgery, undiagnosed adrenal insufficiency poses a significant risk for perioperative blood pressure management and other physiological parameters [8, 9]. Therefore, these risks should be considered during the preoperative assessment of patients who have received neoadjuvant immunotherapy.

Materials and methods

This retrospective study analyzed patients treated at Western General Hospital, Edinburgh, United Kingdom, between March 2023 and December 2024. Patients included in the study were those diagnosed with TNBC who received neoadjuvant chemotherapy in combination with pembrolizumab according to the PEMBRO 3WK R1506 protocol. All patients subsequently underwent preoperative assessment followed by surgery. Patients with metastatic disease were excluded from the study. Data were collected on patient characteristics, clinical and histopathological breast cancer characteristics, treatment timing, preoperative assessment, surgery, blood test results, surgical intervention, postoperative complications, and adverse events. Baseline and clinical characteristics are summarized in Table 1.

Surgical intervention types included wide local excision (WLE), mastectomy, mammoplasty, and axillary surgery, including sentinel node biopsy (SNB), total axillary dissection (TAD), and axillary node clearance (ANC).

Blood work focused on renal function, including serum sodium, potassium, and creatinine; thyroid function, including thyroid-stimulating hormone (TSH) and free thyroxine (free T4); and adrenal function, including serum cortisol, as part of routine preoperative testing. The timing of blood test monitoring was also recorded and related to the completion dates of neoadjuvant pembrolizumab and surgery.

The duration of neoadjuvant pembrolizumab was recorded, including early termination due to adverse events or associated toxicity.

Statistical analysis

Data were analyzed descriptively. Continuous variables are presented as median and range where available, and categorical variables are presented as number and percentage. No hypothesis testing was performed because of the small single-center cohort and the protocol-development purpose of the study.

Table 1. Clinical and histopathological characteristics of the study cohort (n=28)

Characteristic	n	%
Histological subtype		
NST	24	86
Other	4	14
Histological grade		
1	0	0
2	3	11
3	25	89
Hereditary genes		
BRCA1	2	7
BRCA2	2	7
PALB2	1	4
TNM		
T1	3	11
T2	21	75
T3	3	11
T4	1	4
N0	15	54
N1	13	46
M0	28	100
M1	0	0
Immunotherapy-related toxicities		
None	20	71
Pneumonitis	2	7
Colitis	1	4
Skin toxicity, grade 1	0	0
Skin toxicity, grade 2	0	0
Skin toxicity, grade 3	2	7
Hepatitis	1	4
Hypophysitis	1	4
Adrenal insufficiency	1	4
Pre-existing thyroid dysfunction		
Hypothyroid on levothyroxine replacement	5	18
None known	23	82
Preoperative endocrine assessment		
Thyroid function tests between neoadjuvant treatment and surgery	17	61
Cortisol test in immediate preoperative window	1	4
Surgical intervention		
WLE + SNB	18	64
WLE + TAD/ANC	4	14
Mastectomy + SNB/TAD/ANC	6	21
Postoperative surgical complications		
None	25	89
Seroma	2	7
Hematoma	1	4

ANC: axillary node clearance, NST: no special type, SNB: sentinel node biopsy, TAD: total axillary dissection, TNM: tumor-node-metastasis, WLE: wide local excision.

Results

Cohort characteristics

A total of 30 patients with TNBC received neoadjuvant treatment with chemotherapy plus pembrolizumab during the study window from March 2023 through December 2024. Two patients with metastatic disease were excluded, resulting in a final study cohort of 28 patients. The age range of the study cohort was 29-68 years, with a median age of 52 years.

Histological assessment showed that 86% (24/28) of tumors were of no special type (NST), whereas 14% (4/28) comprised other histological subtypes. Histological tumor grade was predominantly grade 3 (89%, 25/28), with three tumors (11%)

classified as grade 2. Five patients had germline mutations, including BRCA1 (n=2), BRCA2 (n=2), or PALB2 (n=1).

TNM classification was reviewed. Most patients (75%, 21/28) had T2 cancer, three patients had T1 disease, three had T3 disease, and one had T4d disease. Involved lymph nodes were observed in 46% (13/28) of patients.

Surgery and postoperative complications

The interval from completion of neoadjuvant treatment, defined as the date of the last cycle, to surgery varied from six to nine weeks. Surgical interventions varied, but most patients underwent breast-conserving surgery.

Length of stay ranged from zero to four days, with a median of one day. Postoperative complications occurred in five patients, including two cases of seroma, one case of hematoma, and one case with postoperative thyroid function test (TFT) derangement.

Immunotherapy treatment and toxicities

A total of 75% of patients completed full neoadjuvant pembrolizumab treatment according to the PEMBRO 3WK R1506 protocol. Overall, 46% (13/28) of patients achieved a pathological complete response (pCR). Eight of 28 patients (29%) discontinued pembrolizumab because of toxicity. Toxicities potentially associated with pembrolizumab included pneumonitis (two cases), colitis (one case), grade 3 skin toxicity (two cases), hypophysitis (one case), hepatitis (one case), hypothyroidism (one case), and adrenal insufficiency (one case).

Preoperative assessment

Presurgical blood testing showed that all patients had preoperative urea and electrolytes (U&E) measured, demonstrating normal serum sodium, potassium, and creatinine levels. Thyroid function was assessed in 96% (27/28) of patients within three months before surgery, with 61% (17/28) having tests between the end of neoadjuvant pembrolizumab/chemotherapy and surgery. Only one patient was diagnosed with hyperthyroidism. Five patients were already receiving thyroxine treatment. Finally, only 36% (10/28) of patients had serum cortisol checked before surgery, one to three months before the final cycle of neoadjuvant treatment, with only one patient (3.5%) having cortisol measured in the immediate preoperative window between the end of neoadjuvant treatment and surgery.

Discussion

Following the results of the KEYNOTE-522 trial, NICE guidance in the United Kingdom has been updated to support consideration of neoadjuvant chemotherapy regimens containing the checkpoint inhibitor pembrolizumab for patients with higher-risk TNBC. This approach has improved both event-free survival and rates of pathological complete response. Despite these benefits, immunotherapies such as pembrolizumab may be associated with significant toxicities and adverse events. The toxicity profile of pembrolizumab is wide-ranging and complex and includes immunosuppression, skin reactions, rheumatological problems, hepatic, pulmonary, pancreatic, cardiovascular, renal, gastrointestinal, ophthalmic, and hematological manifestations, and endocrinopathies. Endocrinopathies are the focus of this study and most commonly manifest as hypophysitis, thyroid dysfunction, or adrenal insufficiency.

These complications are particularly important in patients with early TNBC who undergo surgery under general anesthesia within weeks of completing neoadjuvant treatment. The concern arises from well-documented complications that may occur when these conditions are undiagnosed at the time of anesthesia induction and surgery. These conditions have been linked to several anesthesia-related risks, including difficult blood pressure management and, in some cases, fatal outcomes. Furthermore, the physiological impact of surgery can exacerbate undiagnosed endocrinopathies and perpetuate hemodynamic instability.

Given the risk of these complications after immunotherapy and the increased risk of proceeding to anesthesia and surgery in patients with potentially undiagnosed endocrinopathies, we propose a practical screening protocol. This approach is designed to initiate thyroid and adrenal testing preoperatively and to provide guidance on appropriate management.

In our cohort, 61% of patients had appropriate thyroid function testing at the time of preoperative assessment, whereas only one patient had cortisol measured in the immediate preoperative window. A total of 36% of patients had cortisol levels checked during neoadjuvant treatment as part of routine admission blood tests when they presented to the Cancer Admissions Unit (CAU) with unrelated symptoms while on treatment. The most common reason for admission was pyrexia and other infective symptoms. Overall, two patients were diagnosed with adrenal axis deficiency. On both occasions, these diagnoses were made incidentally when the patients attended the CAU with pyrexia. These patients could otherwise have proceeded to surgery and anesthesia with potentially dangerous undiagnosed endocrinopathies. Implementing a protocol to identify these complications may help reduce risk in this patient group.

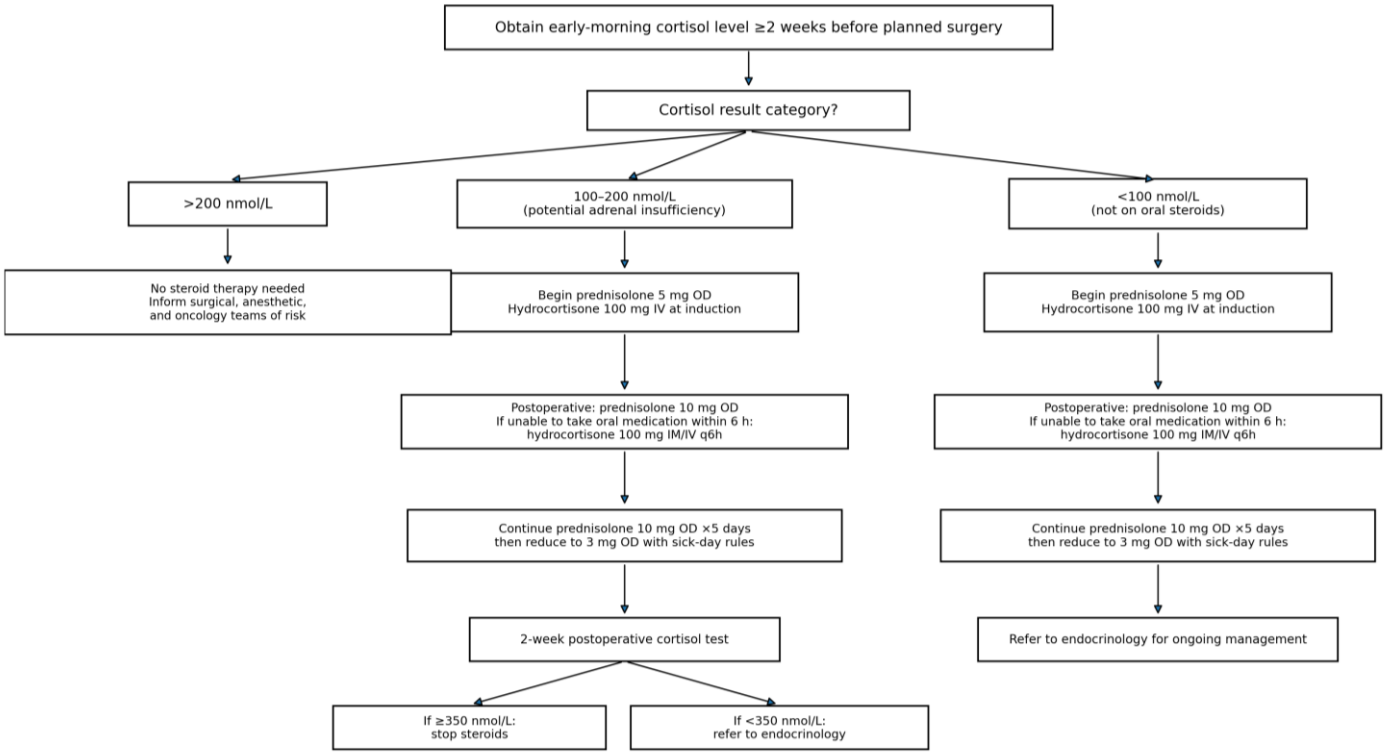
Limitations of this study include its single-center design, which may limit generalizability, and its retrospective nature, which precluded standardized clinical evaluation and may introduce observer bias. The small sample size limits statistical power, and the absence of standardized timing for endocrine testing introduces potential detection bias. Future work should consider prospective data collection, a control group, and assessment of confounding variables.

Review of literature

Thyroid disorders

Hypothyroidism is important to identify in the perioperative period because thyroid hormone homeostasis is closely linked to cardiovascular, respiratory, renal, and gastrointestinal function [4]. With respect to cardiovascular effects, evidence suggests that patients with hypothyroidism may exhibit a 30%-50% reduction in cardiac output, which may contribute substantially to intraoperative and postoperative hypotension [4, 10, 13]. Gastrointestinal complications are also a concern because patients with hypothyroidism frequently have reduced gastrointestinal motility, which poses postoperative challenges and may contribute to ileus, particularly when compounded by opioid use. Reduced motility may also be a concern during anesthetic induction [4, 10, 11]. From a respiratory standpoint, low thyroid function has been associated with

Figure 1. Protocol flowchart for preoperative cortisol assessment



diminished spontaneous ventilation and blunted hypoxic and hypercapnic drive, thereby increasing the risk of postoperative atelectasis and respiratory infections [10, 12-14]. Although direct evidence linking hypothyroidism to increased infection rates in breast surgery is limited, other surgical fields have demonstrated impaired wound healing in patients with hypothyroidism. Finally, although rare, myxedema remains a critical consideration because it is potentially life-threatening [15].

Adrenal dysfunction

A recent large-scale retrospective cohort study of patients with adrenal insufficiency demonstrated an increased risk of all-cause mortality, with risk ratios of 2.19 for men and 2.86 for women. The risk was more strongly associated with primary adrenal insufficiency; although cardiovascular disease was the major cause of mortality, adrenal crisis was also identified as a common cause. The authors concluded that avoidance of adrenal crisis is essential to reducing mortality [16]. Studies have reported that up to 8% of patients with known adrenal insufficiency experience adrenal crisis during inpatient stays [17]. Adrenal crisis can lead to loss of vasomotor tone, hypotension, and profound hyponatremia [9, 18, 19].

Primary adrenal insufficiency is an increasingly recognized adverse event that can present acutely, with a reported incidence of 1%-2% [5, 6]. It has been associated with fatalities resulting from life-threatening adrenal crisis and vasodilatory shock [7]. Onset varies widely from a few days to more than 12 months [6]. In patients undergoing anesthesia, undiagnosed adrenal insufficiency poses a significant risk in terms of blood pressure management and other physiological parameters [8, 9]. Furthermore, surgical stress is known to exacerbate this physiology [20].

Suggested protocol for preoperative management of patients receiving pembrolizumab

An early-morning serum cortisol test should be performed at least two weeks before surgery. If the cortisol level is greater than 200 nmol/L, no steroid replacement is required. Surgical, anesthetic, and oncology teams should be aware of pembrolizumab use and the associated adrenal insufficiency risk on the day of surgery.

If the cortisol level is between 100 and 200 nmol/L, indicating potential adrenal insufficiency, prednisolone 5 mg once daily should be initiated. Perioperatively, hydrocortisone 100 mg should be administered intravenously at induction, followed by a switch to prednisolone 10 mg once daily when the patient is able to eat and drink. If the patient is unable to take oral medication within six hours of induction, hydrocortisone 100 mg should be administered intramuscularly or intravenously every six hours. Prednisolone 10 mg once daily should be continued for five days after surgery and extended if recovery is delayed; it should then be reduced to prednisolone 3 mg once daily with sick-day rules. At two weeks postoperatively, steroids should be stopped if the cortisol level is greater than 350 nmol/L, whereas a cortisol level below 350 nmol/L should prompt referral to endocrinology.

If the cortisol level is less than 100 nmol/L and the patient is not on oral steroids, adrenal insufficiency is likely, and prednisolone 5 mg once daily should be initiated. Perioperative management in this group consists of hydrocortisone 100 mg intravenously at induction, followed by prednisolone 10 mg once daily when oral intake is possible, or hydrocortisone 100 mg intramuscularly or intravenously every six hours if oral medication cannot be taken within six hours of induction. Prednisolone 10 mg once daily should be continued for five days after surgery and extended if recovery is delayed; it should then be reduced to prednisolone 3 mg once daily with sick-day rules,

and the patient should be referred to endocrinology for ongoing management.

If thyroid function tests are abnormal at any stage, urgent referral to endocrinology should be made, and specialist advice should be awaited before proceeding with surgery. Subsequently, long-term thyroid monitoring should be arranged through endocrine follow-up. The protocol is summarized in Figure 1.

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