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Structured endocrine surveillance identifies isolated ACTH deficiency during perioperative pembrolizumab for early triple- negative breast cancer

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Short Report

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Abstract

Isolated ACTH deficiency (IAD) may be underrecognized during perioperative pembrolizumab because symptoms overlap with chemotherapy toxicity. In a retrospective cohort of 17 patients with early triple-negative breast cancer who completed or permanently discontinued KEYNOTE-522–based therapy, 5 (29.4%; 95% CI, 10.3–56.0%) developed endocrinologist-confirmed IAD. All underwent dynamic pituitary testing and received hydrocortisone; 2 subsequently completed all 9 postoperative pembrolizumab cycles. These findings suggest that surveillance intensity and diagnostic classification may substantially influence detection of central adrenal dysfunction.

Introduction

Pembrolizumab combined with neoadjuvant chemotherapy followed by postoperative pembrolizumab improves outcomes in stage II–III triple-negative breast cancer (TNBC).1–3 Endocrine immune-related adverse events (irAEs), however, can be difficult to distinguish from chemotherapy toxicity. In KEYNOTE-522, immune-mediated adrenal insufficiency and hypophysitis were reported in 2.6% and 1.9% of pembrolizumab-treated patients, respectively.4 Real-world reports show heterogeneous adrenal insufficiency rates of 1.9%, 8.6%, and 10.7%.5–7 We therefore characterized isolated ACTH deficiency (IAD) in a consecutive institutional cohort with structured endocrine surveillance.

Methods

This retrospective single-center study included consecutive patients with TNBC who initiated KEYNOTE-522–based perioperative pembrolizumab at Japanese Red Cross Shizuoka Hospital between January 2023 and July 2026. Twenty-five patients initiated therapy; 17 had completed or permanently discontinued perioperative systemic therapy by the prespecified July 31, 2026 cutoff and constituted the mature cohort. Patients received pembrolizumab with paclitaxel/carboplatin followed by pembrolizumab with epirubicin/cyclophosphamide and surgery, with postoperative pembrolizumab when clinically appropriate. ACTH and cortisol were measured before pembrolizumab. Scheduled monitoring was initially approximately every 3 months and changed to monthly after IAD was encountered; testing was also performed promptly when adrenal insufficiency was suspected. All patients diagnosed with IAD were evaluated by endocrinologists and underwent combined CRH, TRH, and GnRH stimulation testing after stabilization, with hydrocortisone withheld for at least 18 hours before testing. irAEs were graded using CTCAE version 5.0. Analyses were descriptive; an exact binomial 95% CI was calculated for the observed IAD proportion. The institutional ethics committee approved the study with an opt-out approach.

Results

Among 17 patients (median age, 56 years; range, 41–83), 9 (52.9%) experienced at least one grade ≥ 2 irAE, accounting for 11 events. IAD occurred in 5 patients (29.4%; exact 95% CI, 10.3–56.0%),

pneumonitis in 4, hepatitis in 1, and colitis in 1. Eleven patients (64.7%) achieved pathological complete response. IAD developed 50–242 days after pembrolizumab initiation (Table 1). At onset, cortisol ranged from 0.06 to 3.29 μg/dL and ACTH was ≤ 3.6 pg/mL. Two events were grade 3 and 3 were grade 2. All 5 patients underwent endocrinology evaluation and dynamic pituitary testing and received hydrocortisone replacement. Pembrolizumab was continued after IAD in 2 patients, both of whom completed all 9 planned postoperative cycles while receiving hydrocortisone. In the other 3, pembrolizumab was not resumed because of patient preference, concomitant grade 4 hepatitis, or individualized risk–benefit assessment. The timing of IAD and other grade 2 or higher irAEs relative to pembrolizumab initiation and surgery is shown in Fig. 1.

Table 1
Clinical characteristics and management of patients with isolated ACTH deficiency

Case/Age	Symptoms; Grade	Days to onset	ACTH before → onset, pg/mL	Cortisol before → onset, μg/dL	Pituitary MRI	Pembrolizumab after IAD
1; 56 y	Fever, fatigue; G3	139	15.4 → <1.5	14.17 → 1.44	No abnormality	Not resumed; patient preference
2; 57 y	Fever, fatigue; G2	242	25.5 → <1.5	18.56 → 2.77	No abnormality	Not resumed; Grade 4 hepatitis
4; 60 y	Dizziness; G2	98	11.4 → 3.6	15.72 → 0.635	No abnormality	Continued; completed 9 postoperative cycles
5; 58 y	Drowsiness; G2	154	42.9 → <1.5	12.31 → 0.06	Possible pituitary stalk enlargement	Continued; completed 9 postoperative cycles
14; 83 y	Fever, diarrhea; G3	50	12.6 → <1.5	7.91 → 3.29	Unknown	Not resumed; individualized risk-benefit assessment

ACTH, adrenocorticotropic hormone; G, grade; IAD, isolated ACTH deficiency. All 5 patients underwent endocrinology evaluation and combined CRH, TRH, and GnRH stimulation testing after clinical stabilization and received hydrocortisone replacement.

Discussion

The principal observation is a marked discrepancy between the frequency of rigorously characterized IAD in this cohort and adrenal toxicity reported in KEYNOTE-522. The 29.4% estimate is imprecise and should not be interpreted as population incidence. Nevertheless, variation across real-world cohorts and an I-SPY2 analysis reporting adrenal insufficiency in 11.8% across neoadjuvant immune-checkpoint inhibitor regimens8 suggest that ascertainment may materially affect reported rates. Terminology also

complicates comparison: adrenal insufficiency, hypophysitis, and IAD are not interchangeable. Here, low or inappropriately low ACTH with low cortisol prompted specialist assessment, and all 5 cases underwent dynamic pituitary testing. Structured surveillance may therefore identify central adrenal dysfunction that might otherwise be attributed to chemotherapy or other irAEs. This remains hypothesis-generating because monitoring intensified after the first IAD cases. IAD also did not uniformly require permanent pembrolizumab discontinuation: 2 patients completed postoperative therapy with hydrocortisone replacement. Limitations include the retrospective single-center design, small mature cohort, wide confidence interval, changing surveillance schedule, and selection of patients with mature treatment outcomes. Prospective studies with standardized ACTH/cortisol surveillance and uniform diagnostic criteria are needed to determine whether IAD during perioperative pembrolizumab is underrecognized.

Declarations

Data availability

Individual-level participant data are not publicly available because of patient privacy and re-identification concerns in this small single-center cohort. Aggregate data supporting the findings are contained within the article. Further information may be available from the corresponding author subject to institutional and ethics requirements.

Competing interests

The authors declare no competing interests.

Ethics approval

The institutional ethics committee of Japanese Red Cross Shizuoka Hospital approved this retrospective study. An opt-out approach was used in accordance with the approved protocol.

Consent to participate:

The requirement for individual written informed consent was waived by the institutional ethics committee because of the retrospective nature of the study. Information about the study was disclosed to eligible participants, who were provided the opportunity to opt out, in accordance with the approved protocol.

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Author Contribution

M.K. conceived and designed the study, acquired, analyzed, and interpreted the data, and drafted the manuscript. H.M. contributed to data acquisition and interpretation. K.Y. and N.H. contributed to endocrine evaluation, interpretation of the clinical data, and critical revision of the manuscript. R.M. contributed to study design, data interpretation, and supervision. All authors critically reviewed and approved the final manuscript.

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Figures

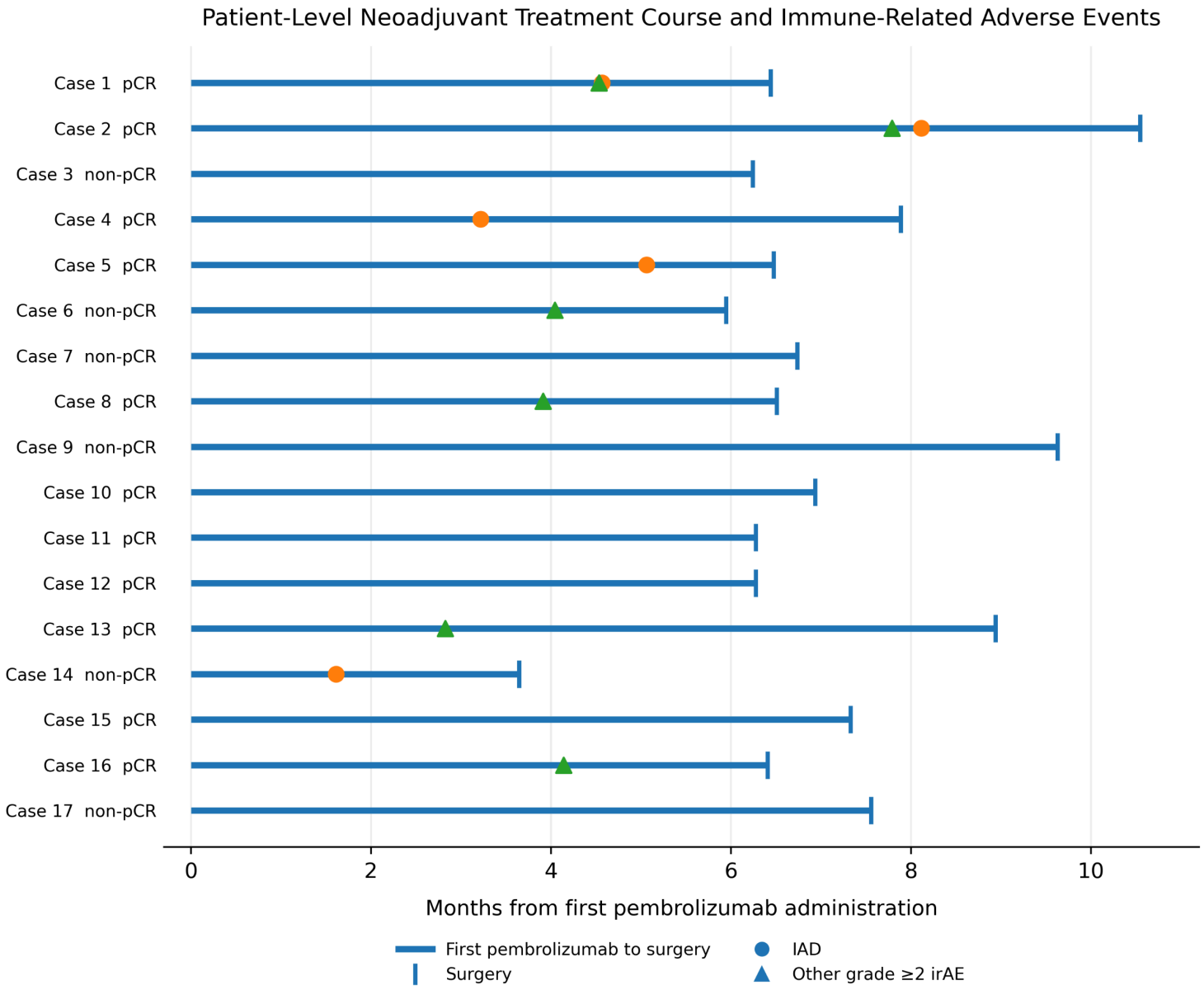


Figure 1

Patient-level neoadjuvant treatment course and immune-related adverse events

Time is measured from the first pembrolizumab administration to surgery for each of the 17 patients in the mature cohort. Circles indicate IAD, triangles indicate other grade ≥2 immune-related adverse events, and vertical markers indicate surgery. Pathological complete response status is shown beside each case.