**Corrected: Exploring a New Entity of Single-Agent Pembrolizumab-Associated Hypophysitis**

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This article has been corrected.

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This article has been corrected to accurately reflect author Vibeke Kruse’s affiliations. The following affiliations have been added:

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The authors deeply regret that this was not noticed prior to publication.

**Abstract**

Hypophysitis is the inflammation of the pituitary gland primary or secondary to local or systemic disease. It tends to occur more with cytotoxic T-lymphocyte-associated protein 4 inhibitors (10-15% of cases), which is a different entity compared to that associated with anti-program death 1 (anti-PD1) inhibitors. We describe a case of pembrolizumab-associated hypophysitis and conduct a systematic review of the literature.

A 55-year-old woman with stage pT3aN1a (TNM stadium IIIb) melanoma presented with headache, nausea and fatigue three and a half months after starting pembrolizumab. Blood analyses revealed secondary adrenal failure, thyrotropic insufficiency and defective gonadotrophin secretion. An imaging study showed an enlarged pituitary gland with a homogeneous enhancement of the gland and pituitary stalk. Interruption of anti-PD1 therapy and administration of hormonal supplementation lead to clinical, biological and radiologic improvement after eight months.

We identified 17 studies (20 patients) on single-agent pembrolizumab-associated hypophysitis. Patients were treated for melanoma (n=7; 33.3%), urogenital (n=5; 23.8%), lung (n=4; 19.0%), larynx (n=1; 4.8%), pharynx (n=1; 4.8%), breast (n=1; 4.8%) and colon (n=1; 4.8%) neoplasia. The time to onset of pituitary insufficiency was most frequently six months (range 1.5-39.0 months) after treatment initiation. The most prevalent hormonal defect was isolated adrenocorticotropic hormone (ACTH) deficiency. Four cases were reported with multiple central hormonal defects. In those patients, an enlarged pituitary gland was also observed.

Our case has distinct features, including early disease onset after single-agent pembrolizumab initiation, panhypopituitarism and increased pituitary mass. These findings are in contrast with the majority of other cases of pembrolizumab-induced hypophysitis, as most patients present an isolated ACTH deficiency. Whether or not this is a new clinical entity warrants further investigation.

**Categories:** Endocrinology/Diabetes/Metabolism, Internal Medicine, Oncology

**Keywords:** gonadotropin insufficiency, thyrotropic failure, corticotropin deficiency, anterior pituitary failure, autoimmune hypophysitis, pembrolizumab, immune checkpoint inhibitors

**Introduction**

Pembrolizumab is an anti-programmed cell death protein 1-specific (anti-PD-1) monoclonal antibody used in monotherapy or combination therapy for several types of malignancies. Immune-related adverse events
may occur in patients treated with anti-PD-1 monoclonal antibodies due to immune system activation. However, hypophysitis is a rarely reported adverse effect of anti-PD-1 monotherapy. Early recognition and treatment of immune-induced hypophysitis are important to prevent life-threatening complications mostly due to secondary adrenal failure [1-3]. In line with this foreword, we describe the clinical course of single-agent pembrolizumab-induced hypophysitis in a 55-year-old woman treated for malignant melanoma. Distinct clinical features were observed, including early onset after starting pembrolizumab, deficiency in three pituitary axes (adrenocorticotropic, thyrotropic and gonadotrophic axis) and increased pituitary mass.

Case Presentation

A 55-year-old woman presented with headache, nausea and fatigue ongoing for two weeks. Seven months prior to the current episode, she was diagnosed with a stage pT3aN1a (TNM stadium IIIb) malignant melanoma of the right groin. Molecular testing did not find a BRAF or NRAS mutation. Surgical excision and removal of the sentinel node were performed. Adjuvant single-agent therapy with pembrolizumab 2 mg/kg every three weeks for one year was subsequently initiated. After just five cycles of immunotherapy, she presented with the symptoms mentioned above. She did not report increased thirst, polyuria or nocturia. On examination, systemic blood pressure was 155/79 mmHg, heart rate was 72 beats per minute, oxygen saturation was 98% on room air and temperature was 35.5°C. Further physical examination was unremarkable.

Initial laboratory findings are shown in Table 1. ACTH deficiency was observed as well as secondary hypothyroidism and hypogonadotropic hypogonadism. Very low levels of morning cortisol and ACTH at 0.5 mg/dL (normal range: 6.0 to 30.0 mg/dL) and <5.0 pg/mL (normal range: 10 to 60 pg/mL), respectively, were substantiated on blood analysis. TSH and peripheral thyroid hormone (free T4 and T3) levels also declined after pembrolizumab initiation (Figure 1). Analysis of the gonadotropic axis showed LH lower than 0.2 U/L (normal range: 1.1 to 52.4 U/L) and low FSH at 0.97 U/L (normal range: 5.9 to 72.8 U/L). Growth hormone and IGF-1 levels were normal (Table 1). Likewise, the sodium level was normal. The absence of typical clinical symptoms argued against altered posterior pituitary function. Anti-thyroid peroxidase antibodies were negative.

| Hormone            | Patient’s value | Normal range       |
|--------------------|-----------------|--------------------|
| Morning ACTH       | < 5.0 pg/mL     | 8:00 am: 10-60 pg/mL |
| Morning cortisol   | 0.5 mg/dL       | 8:00 am: 6.0-30.0 mg/dL |
| TSH                | 0.25 mU/L       | 0.35-4.50 mU/L     |
| fT4                | 5.1 pmol/L      | 9.3-23.2 pmol/L    |
| fT3                | 3.72 pmol/L     | 3.30-6.10 pmol/L   |
| LH                 | < 0.2 U/L       | 1.1-52.4 U/L       |
| FSH                | 0.97 U/L        | 5.9-72.8 U/L       |
| Oestradiol         | < 11.0 ng/L     | 11-462.1 ng/L      |
| CRP                | 16.1 mg/L       | < 3.0 mg/L         |
| IGF-1              | 88.6 ng/mL      | 44.7-210.0 ng/mL   |
| Growth hormone     | 1.78 mg/dL      | < 8.0 mg/dL        |
| Sodium             | 138 mmol/L      | 135-145 mmol/L     |

**TABLE 1: Biological characteristics of the reported case at the time of onset of pembrolizumab-induced auto-immune hypophysitis**

ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, fT4: free tetraiodothyronine, fT3: free triiodothyronine, LH: luteinizing hormone, FSH: follicular stimulating hormone, CRP: C-reactive protein, IGF-1: insulin-like growth factor 1
FIGURE 1: Time-dependent variation of thyroid stimulating hormone (blue line) and peripheral free tetraiodothyronine (red line) from the start of treatment with pembrolizumab (T0)

The arrow indicates the time of onset of pituitary failure, including secondary hypothyroidism.

* Levothyroxine 50 µg/day 5/7 days and 100 µg 2/7 days

Gadolinium-enhanced magnetic resonance imaging (MRI) showed an enlarged pituitary gland (12.95 mm x 15.65 mm x 11.04 mm) with the homogeneous enhancement of the gland and the enlarged pituitary stalk (Figures 2A-2B). There was also a very discrete dural enhancement posterior of the sella turcica on the post-contrast images.
FIGURE 2: T1-weighted fluid-attenuated inversion recovery (FLAIR) sagittal MRI imaging features of the pituitary gland (thick arrows) and stalk (thin arrows) at diagnosis (A and B, respectively), three (C and D, respectively) and eight months after interruption of Pembrolizumab (E and F, respectively)

An increased hypothalamic signal was observed on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images (not shown). Neurohypophysis depicted normal signals.

Differential diagnosis

In our case, a number of differential diagnoses were excluded. Among those, primary hypophysitis typically occurs in younger women during pregnancy or the peripartum period [4-5]. It tends to induce more enlargement of the pituitary gland than immunotherapy-induced hypophysitis (IIH). Pituitary size in IIH is typically less than two centimetres. Because of the greater size, patients with primary hypophysitis present more often with headaches and visual disturbances than patients with IIH [5]. This was not the case with our patient.

Pituitary lesions, such as adenoma, craniopharyngioma or Rathke’s cleft cyst, were ruled out in the imaging study. Moreover, the hypothalamic-pituitary-adrenal axis is usually affected last in such lesions [4].

Metastasis is another important differential diagnosis to rule out given the oncological context. The prevalence of isolated pituitary metastases is very low and accounts overall for only 0.4% of all intracranial metastases. Additionally, melanoma causes only 2% of all pituitary metastases [6]. In our case, there was a homogeneous enhancement of the pituitary gland, whereas heterogeneous enhancement is more typical for metastases [7].

Lastly, the clinical presentation of immunoglobulin G4 (IgG4)-related hypophysitis is very similar to IIH, but it was ruled out in our case based on the negative biochemical measurement of IgG4. Inconsistent with our case, the multisystemic disease is a more common presentation of IgG4-related disease. Isolated pituitary involvement is reported in only 4-5% of patients [4].

Management

The patient was initially treated with high-dose intravenous hydrocortisone substitution therapy, which was reduced to 25 mg hydrocortisone daily after seven days. Education on sick day rules and appropriate stress dosing was given. Thyroxine replacement with Levothyroxine 50 µg per day was initiated. According to international guidelines, checkpoint inhibition can be continued despite the development of an immune-related endocrinopathy, but this patient decided to interrupt treatment for personal reasons [8].

Outcome and follow-up

Symptoms drastically improved under replacement therapy. After three months of hormonal substitution and interruption of pembrolizumab, positron emission tomography of the head, thorax and abdomen as well as a new pituitary MRI showed no tumour recurrence or distant metastasis. Because of the stable disease, no
alternative treatment was administered to optimise the control of the primary oncological disease (melanoma). MR images showed a reduced swelling of the pituitary gland and stalk after three months (Figures 2C-2D), and after eight months (Figures 2E-2F), no stigmata of residual inflammation could be observed. However, a small hypodense lesion between the anterior and posterior pituitary glands was reported. At the time of this report, one year after discontinuation of pembrolizumab, the patient remains clinically stable.

Discussion
Immune checkpoint inhibitors are increasingly used in the treatment of various cancers. Therefore, immune-related adverse events are prevalent, including those affecting endocrine glands. Hypophysitis secondary to single-agent anti-PD-1-inhibitors, such as the most commonly used pembrolizumab and nivolumab, is very rare. The estimated incidence amounts to 0.5% of treated cases [2]. This is noticeably lower compared to that of hypophysitis due to anti-CTLA-4-inhibitors, which is estimated to be 10-15% [9-10]. Overall, little data is available on pembrolizumab-induced hypophysitis and consist mostly of case reports, series and letters.

For comparison with our case, we conducted a systematic review of studies in MEDLINE from inception to 27/01/2022 using the search terms "hypophysitis", "pituitary failure", "pituitary insufficiency" and "pembrolizumab". Data were selected from relevant studies according to variables described further in the study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection is depicted in Figure 3. We identified 17 papers reporting 20 patients with single-agent pembrolizumab-induced hypophysitis.

FIGURE 3: PRISMA flow chart summarizing studies identification, screening and selection
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Clinical presentation
The time to onset after initiation of pembrolizumab therapy is about six months in most cases (range 1.5 to 39 months). Case reports by Boudjemaa et al. and Yamagata et al. suggest that auto-immune toxicity can develop even after treatment withdrawal, showing the importance of follow-up even after ending the treatment [11-12].

Patients with single-agent anti-PD-1 hypophysitis presented most frequently with general symptoms such as fatigue, anorexia, nausea and vomiting [13]. Patients were treated for melanoma (n=7; 35.3%), urogenital (n=5; 23.8%), lung (n=4; 19.0%), larynx (n=1; 4.8%), pharynx (n=1; 4.8%) and breast (n=1; 4.8%) and colon
Hormonal disturbances

Anti-PD-1 hypophysitis is most commonly associated with isolated ACTH deficiency. This involves most frequently the hypothalamic-pituitary-adrenal axis. Defects of the neurohypophysis are mainly reported in the context of pituitary metastasis [4]. Ascertainment of secondary adrenal failure used different testing strategies, including morning cortisol and ACTH [9,11-12,15,17-21], short Synacthen test [12,16,18-21] and corticotropin-releasing hormone (CRH) stimulation test [12,16,24]. In our patient, three pituitary axes were affected: the adrenocorticotrophic, thyroid and gonadotrophic axes. This is a rather rare presentation reported in three other patients in the currently available literature [20-22,27]. The time to onset was relatively short and ranged from three to nine months and two of the patients were diagnosed with melanoma [14]. Unlike our patient, the case reported by Malikova et al. presented another auto-immune adverse event involving the lungs (pneumonitis) [22]. However, based on the limited number of cases, one cannot accurately infer the risk of other organs’ involvement when multiple hormonal axes are impaired or the other way around. This seems not to be the case since independently of the number of hormonal axes involved, immune adverse events in other sites have been reported (Table 2) [9,11-12,15,17,19,21,25,28].

| Author, Year | No | Age/Sex | Primary Tumor | Time of MN | Symptoms | Laboratory Findings | Pituitary MRI | PANR other than ACTH deficiency |
|-------------|----|---------|---------------|------------|----------|-------------------|-------------|-----------------------------|
| Latcher, 2020 [10] | #1 | 75M | Metastatic urothelial cancer | 3.0 months | Severe fatigue, cost interstition | Baseline ACTH 54 pg/mL, Random cortisol 21 µg/dL, Week 3: ACTH 13 µg/mL, Random cortisol 3 µg/dL | Not available | Not available |
| Goodwinth, 2021 [10] | #2 | 58F | Metastatic urothelial cancer (high-grade urothelial pT1 cancer) | 6.0 months | Generalized fatigue, appetite loss, abdominal pain, altered mental status | ACTH 26 pg/mL, Cortisol 0.7 µg/dL | Not available | Central hypopituitarism and hypogonadism |
| Hotta, 2021 [10] | #3 | 78F | Metastatic urothelial cancer | 5.5 months | Anorexia, general weakness, back pain, muscle pain in extremities, difficulties walking | ACTH 16.6 pg/mL, Cortisol 1.4 µg/dL, SST: 0.82 mIU/mL, ACTH 0.82 mIU/mL, Cortisol 0.92 µg/dL | Normal | Normal |
| Peric, 2019 [17] | #4 | 71M | Transitional cell carcinoma | 6.0 months | Fatigue, anorexia, diarrhea, myalgia, depression | ACTH 13.1 pg/mL, Cortisol 1.16 µg/dL | Normal | Normal |
| Boudjemaa, 2018 [11] | #5 | 62F | Stage IV large cell lung carcinoma (1T2N2M1a) | 20.0 months | Fatigue, appetite loss, weight loss, nausea, pain in both shoulders | ACTH 0.805 pg/mL, Random cortisol 0.302 µg/dL, SST: unsatisfactory contact response | Normal | Subclinical primary hypothyroidism |
| Tarakla, 2020 [10] | #6 | 62F | Stage IV squamous cell lung cancer (T3N0M1a) | 6.0 months | Fatigue and loss of appetite | ACTH 2.39 mIU/mL, Cortisol 11.07 µg/dL, TSH 0.92 µg/dL, ft4 0.92 pmo/L | Normal | Normal |

(n=1, 4.8%) neoplasms. This non-specific clinical presentation is often difficult to distinguish from the underlying oncological pathology in which such symptoms are common [14]. This could lead to delayed diagnosis [2]. However, concurrent hyponatremia could increase the clinical suspicion index of those symptoms as previously reported by others [9,13-19]. In our case, headaches but not visual disturbances were one of the presenting symptoms. Other potential etiologic factors of headache including metastasis were ruled out.
| #    | Age | Sex | Diagnosis                                      | Duration | Symptoms/Signs                                                                                       | Laboratory Tests/Imaging Findings                                                                                     | Course/Outcome                                                                                     | Notes                                                                 |
|------|-----|-----|-----------------------------------------------|----------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| #5   | 68M |     | Relapsed adrenal metastatic non-seed lung carcinoma | 7.5 months | Anorexia, fatigue, fever<br>ACTH: 17.2 pg/mL, Cortisol: 0.89 µg/dL<br>CRH test: Peak ACTH 29.3 pg/mL, Cortisol 3.1 µg/dL, 30' 2.3 µg/dL, 60' 7.6 µg/dL<br>24-h urinary cortisol: undetectable. | Baseline: Normal thyroid function and TPO-Ab and anti-TSH pos.<br>Month 6: Primary hypothyroidism<br>During LI-thyrome therapy: TSH 8 mIU/L, fT4 12.23 pmol/L, TgAb pos, TPOAb pos | Pembrolizumab 6.0 months<br>Onset 4.0 months<br>7.5 months after Pembrolizumab discontinuation | Secondary hypothyroidism, Minor skin rash |
| #6   | 65M |     | Metastatic melanoma                           | 10.5 months| Headache, severe muscle weakness<br>ACTH < 5 pg/mL, Cortisol 0.4 µg/dL | TSH 0.049 mIU/L, fT4 not specified<br>Cortisol: 0.6 µg/dL, 24-h urinary cortisol: undetectable. | Pembrolizumab 16.0 months<br>16.0 months after discontinuation | Primary hypothyroidism |
| #10  | 66F |     | Metastatic melanoma                           | 3.0 months | Headache, fever, fatigue, cough, anorexia<br>ACTH 4.44 pg/mL, Cortisol 1.34 µg/dL | TSH 0.049 mIU/L, fT4 not specified<br>Cortisol: 0.6 µg/dL, 24-h urinary cortisol: undetectable. | Pembrolizumab 25.5 months<br>25.5 months after discontinuation | Secondary hypothyroidism |
| #11  | 24F |     | Metastatic melanoma                           | 25.5 months| Nausea, vomiting<br>Coricostroph defect without further specification | Not specified | Pembrolizumab 25.5 months<br>25.5 months after discontinuation | Primary hypothyroidism |
| #12  | 66M |     | Melanoma                                      | 16.0 months| Fatigue, anorexia, weight loss<br>ACTH 11.8 pg/mL, Cortisol 4.20 µg/dL<br>CRH test: Peak ACTH 20.1 µg/dL, Cortisol 2.16 µg/dL, 30' 6.74 µg/dL, 60' 8.10 µg/dL | TSH 3.46 mIU/L, fT4 0.9 pmol/L, T3 5.1 pmol/L | Pembrolizumab 6.0 months<br>Onset 4.0 months<br>6.0 months after discontinuation | Secondary hypothyroidism |
| #13  | 52F |     | Metastatic melanoma (CTx, pHNti, M1)          | 9.0 months | Progressive generalized weakness, extreme fatigue, infarcts, impalpable, poor appetite, weight loss, mood changes<br>ACTH < 1.1 pg/mL, Cortisol 0.2 µg/dL | Not specified | Pembrolizumab 6.0 months<br>Onset 4.0 months<br>9.0 months after discontinuation | No hypothyroidism |
| #14  | 55F |     | Melanoma (pT2N1a)                            | 3.0 months | Headache, nausea and fatigue<br>ACTH 0.5 pg/mL, Cortisol 0.5 µg/dL | TSH 0.24 mIU/L, fT4 0.5 pmol/L, T3 2.35 pmol/L | Pembrolizumab 6.0 months<br>Onset 4.0 months<br>3.0 months after discontinuation | Secondary hypothyroidism and hypogonadism |
| #15  | 75M |     | Melanoma                                      | 6.0 months | Dyaphagia, early satiety, nausea, vomiting, diarrhea, anorexia, weight loss<br>ACTH 2 µg/dL, Cortisol 7.4 µg/dL | TSH 0.001 mIU/L, fT4 11.45 pmol/L | Pembrolizumab 6.0 months<br>Onset 4.0 months<br>6.0 months after discontinuation | Non-hypothyroidism |
| #16  | 78M |     | Metastatic hypopharyngeal cancer             | 7.5 months | Fever, anorexia, vomiting<br>CRH test: no response of ACTH or cortisol | Not specified | Pembrolizumab 9.0 months<br>9.0 months after discontinuation | No hypothyroidism |
| #17  | 51F |     | Breast carcinoma                             | 6.0 months | Fatigue, diarrhoea<br>ACTH < 5 pg/mL, Cortisol < 1.0 µg/dL, SST: Cortisol 0.4 µg/dL, 30': 27.6 µg/dL, 60': 28.7 µg/dL | TSH 2.61 mIU/L, fT4 7.0 pmol/L | Pembrolizumab 6.0 months<br>Onset 4.0 months<br>6.0 months after discontinuation | Primary hypothyroidism |

**Notes:**<br>- #14: Case of non-responding ACTH or cortisol<br>- #15: Case of non-responding ACTH or cortisol<br>- #16: Case of non-responding ACTH or cortisol<br>- #17: Case of non-responding ACTH or cortisol
Imaging findings in pembrolizumab-associated hypophysitis

In the absence of a biopsy to ascertain the diagnosis of hypophysitis, imaging studies are critical tools in daily clinical practice. In our case, we describe diffuse enlargement and homogeneous enhancement of the gland as well as moderate enlargement with the enhancement of the pituitary stalk found on magnetic resonance imaging. This is however not a widespread finding since some reported a solitary change in homogeneity or enhancement [18,22] and others normal imaging findings [9,11-12,15,17,19,27]. As previously reported [29], the review of published cases and our case suggest that increased pituitary size is associated with multiple hormonal axis involvement [21,25,27]. As opposed to the enhancement and enlargement of the pituitary stalk, the same changes on the gland seem to be more specific for the diagnosis of hypophysitis using MR imaging and therefore are more accurate for follow-up purposes [30].

Comparison with anti-CTLA-4-associated hypophysitis

Anti-PD-1 hypophysitis, specifically that associated with pembrolizumab, seems to be a different clinical entity than anti-CTLA-4 hypophysitis [14]. According to Faje et al., when treated with pembrolizumab (or nivolumab), patients typically tend to develop hypophysitis later during the course of treatment compared to their ipilimumab-treated counterparts (median 25.8 weeks vs. 9.3 weeks, p < 0.0001) [2].

Another difference between anti-PD-1 therapy and anti-CTLA-4 therapy is the presence of MRI changes. Patients on anti-CTLA-4 therapy usually have an enlargement of the pituitary gland on MRI imaging, which often resolves within a few months [5]. Sometimes, MRI changes may even precede the clinical picture, which we observed in our case. It is recommended to perform MRI imaging at baseline and routinely in the first six months after initiation of immunotherapy. An incidental finding of pituitary enlargement should lead to a biochemical assessment of all pituitary axes. However, pituitary enlargement or other MRI changes are rarely seen after anti-PD-1 monotherapy [2].

On the other hand, similarly to anti-CTLA-4-induced endocrine adverse events [31], except for one patient in whom de-escalation of corticosteroids and thyroid hormone suppletions were considered [27]. All patients with available data required hormonal support after a follow-up time ranging from one to 19 months. In most cases, pembrolizumab was continued [9,17,25]. In some instances, this was after a transient interruption [20,25].
Strengths and limitations
The strengths of the present report include a succinct case description and a systematic review of the literature. Comparison with similar published reports enabled us to identify a common presenting feature that could be characteristic of single-agent pembrolizumab-associated hypophysitis with the involvement of multiple hormonal axes. The absence of pituitary biopsy to ascertain the diagnosis of immune-mediated hypophysitis could be considered a limitation of our study. Nevertheless, the benefit-risk ratio of this diagnostic modality needs to be considered due to its invasive nature [4]. To date, there are no clear recommendations nor clear criteria for considering pituitary biopsy in adults. A biopsy could be requested when the diagnosis is unclear [4]. In our case, clinical and biological evaluations enabled us to rule out potential differentials.

Conclusions
We report a case of single-agent pembrolizumab-induced hypophysitis characterized by early disease onset after anti-PD-1 treatment initiation, panhypopituitarism and increased pituitary mass. These are distinct features compared to the majority of reported cases of single-agent pembrolizumab-induced hypophysitis, as most patients present with an isolated ACTH deficiency. Further exploration to ascertain whether or not this is a new clinical entity warrants further investigation. Until then, clinicians should be aware that hypophysitis induced by single-agent pembrolizumab might cover a heterogeneous clinical spectrum. Prompt identification and treatment remain of great importance to prevent further deterioration.

Additional Information

Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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