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| RESEARCH ARTICLE

Milder Than Expected: Real-World Endocrine Toxicity Profile of Immune Checkpoint Inhibitors in Eastern Algeria

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| ABSTRACT

The recent introduction of immune checkpoint inhibitors (ICIs) in Algeria in late 2024 has transformed the therapeutic landscape for multiple malignancies. While endocrine immune-related adverse events (irAEs) are well-documented globally, real-world data concerning their clinical presentation and severity in the Algerian population remain scarce. This study aims to report the initial experience of endocrine toxicity management following the introduction of PD-1 and PD-L1 inhibitors across a broad spectrum of cancers. We conducted an observational, real-world analysis within a medical oncology department in Eastern Algeria, enrolling patients initiated on ICI therapy since late 2024. The cohort comprised 84 patients distributed across various tumor types and regimens: 60 received pembrolizumab (23 triple-negative breast cancer, 17 non-small cell lung cancer, 9 renal cell carcinoma [RCC], 8 melanoma, 3 gastric cancer); 19 received nivolumab (5 pancreatic cancer, 4 urothelial carcinoma, 3 head and neck cancer, 5 RCC, 2 gastric cancer); 3 received avelumab (RCC); and 2 received atezolizumab (hepatocellular carcinoma). While various potential toxicities were monitored, particular attention was dedicated to endocrine side effects, which mandated the active involvement of endocrinologists in this surveillance framework. All toxicities were graded according to CTCAE v5.0 criteria. Endocrine irAEs were observed within the cohort, with dysthyroidism representing the most frequent manifestation and the primary driver for endocrinological referral. Strikingly, the clinical severity of these endocrine toxicities was notably lower than the profiles typically reported in the international literature. The majority of events were low-grade (CTCAE Grade 1-2), allowing for symptomatic hormonal substitution without necessitating ICI discontinuation. No high-grade (Grade 3-4) endocrinopathies, such as fulminant hypophysitis or adrenal crisis, were documented in this preliminary cohort. In this initial real-world experience from Eastern Algeria, the use of pembrolizumab, nivolumab, avelumab, and atezolizumab across various localizations demonstrates a manageable endocrine safety profile, with toxicities manifesting at a lesser severity than expected. These findings support a favorable risk-benefit ratio; however, the specific impact on thyroid function underscores that ongoing multidisciplinary surveillance—actively integrating endocrinologists—remains imperative to ensure prompt management and treatment continuity.

| KEYWORDS

Immune checkpoint inhibitors, endocrine toxicity, dysthyroidism, pembrolizumab, nivolumab, avelumab, atezolizumab, immune-related adverse events, real-world data, Eastern Algeria.

| ARTICLE INFORMATION

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1. Introduction

The advent of immune checkpoint inhibitors (ICIs), targeting the programmed death-1 (PD-1) receptor and its ligand (PD-L1), has fundamentally reshaped the oncological treatment paradigm across a multitude of malignancies [Sharma and Allison, 2015]. By reinvigorating cytotoxic T-cell responses against tumor antigens, ICIs offer

unprecedented survival benefits. However, this immune activation is frequently unselective, leading to a spectrum of immune-related adverse events (irAEs) that can affect virtually any organ system [Postow et al., 2018].

Among these, endocrine irAEs represent a distinct clinical challenge. Toxicities such as thyroiditis (manifesting as hypothyroidism or transient hyperthyroidism), hypophysitis, primary adrenal insufficiency, and type 1 diabetes mellitus are well-documented in clinical trials [Byun et al., 2023]. Unlike other irAEs that may resolve with immunosuppression, endocrine toxicities often result in permanent glandular destruction, necessitating lifelong hormone replacement therapy [de Filette et al., 2021].

In Algeria, the national oncological landscape entered a new era in late 2024 with the official introduction and reimbursement of several ICIs, including pembrolizumab, nivolumab, avelumab, and atezolizumab. While international landmark trials have established the safety profiles of these agents, substantial heterogeneity exists across different ethnic and geographic populations [Abdel-Rahman and Fouad, 2015]. Real-world data concerning the incidence, clinical presentation, and severity of endocrine irAEs in the North African population remains conspicuously absent. Furthermore, the structural integration of endocrinologists into routine oncological care pathways in developing healthcare systems is often fragmented.

To address this literature gap, we conducted a real-world observational study within a medical oncology department in Eastern Algeria. The primary objective was to evaluate the clinical spectrum and severity of endocrine toxicities following the initiation of ICI therapy across a broad spectrum of cancers. A secondary objective was to assess the impact of a proactive, multidisciplinary surveillance framework—particularly emphasizing thyroid monitoring and endocrinological co-management—on treatment outcomes.

2. Methods

2.1. Study Design and Setting

This was a monocentric, observational, real-world analysis conducted at the Medical Oncology Department, Constantine, Eastern Algeria. The study included all consecutive patients initiated on ICI therapy between December 2024 and May 2025.

2.2. Patient Population

A total of 84 patients were enrolled. Eligibility criteria included: age ≥ 18 years, histologically confirmed advanced or metastatic malignancy, indication for ICI therapy according to national and international guidelines, and at least one clinical and biological endocrine assessment post-infusion. Patients with pre-existing uncontrolled endocrinopathies were excluded from the toxicity analysis but were monitored for exacerbations.

2.3. Treatment Regimens

The cohort was treated according to standard of care protocols:

- **Pembrolizumab (n=60):** Administered at 200 mg every 3 weeks. Indications included 23 triple-negative breast cancers (TNBC), 17 non-small cell lung cancers (NSCLC), 9 renal cell carcinomas (RCC), 8 melanomas, and 3 gastric cancers.
- **Nivolumab (n=19):** Administered at 240 mg every 2 weeks or 480 mg every 4 weeks. Indications included 5 pancreatic cancers, 4 urothelial carcinomas, 3 head and neck squamous cell carcinomas (HNSCC), 5 RCCs, and 2 gastric cancers.
- **Avelumab (n=3):** Administered at 10 mg/kg every 2 weeks for 3 RCC patients.
- **Atezolizumab (n=2):** Administered at 1200 mg every 3 weeks for 2 hepatocellular carcinoma (HCC) patients.

2.4. Endocrine Surveillance and Assessment

A standardized prospective monitoring algorithm was implemented. While various potential endocrine toxicities were monitored, particular attention was dedicated to thyroid side effects, which mandated the active involvement of endocrinologists in this surveillance framework.

Baseline assessments included serum TSH, free T3, free T4, morning cortisol, ACTH, fasting glycemia, and HbA1c. Post-treatment monitoring was conducted every 3 weeks for the first 12 weeks, and every 6 weeks thereafter, or immediately upon symptom onset.

- **Thyroid Function:** Asymptomatic TSH alterations were closely monitored. Symptomatic dysfunction or TSH deviations persisting beyond 6 weeks triggered immediate endocrinological referral.
- **Hypophysitis/Adrenal Insufficiency:** Evaluated in the presence of refractory fatigue, hypotension, hyponatremia, or hyperkalemia.

All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Decisions regarding ICI interruption, systemic corticosteroids, or hormonal replacement were made jointly by the oncologist and endocrinologist.

2.5. Statistical Analysis

Descriptive statistics were utilized. Categorical variables were expressed as frequencies and percentages, and continuous variables as means ± standard deviation (SD) or medians with interquartile ranges (IQR), as appropriate. All analyses were performed using SPSS software (Version 28.0, IBM Corp, Armonk, NY).

3. Results

3.1. Patient Demographics and Baseline Characteristics

Of the 84 patients included, the median age was 61 years (range: 34–78), with a slight male predominance (54.8%), largely reflecting the epidemiology of the treated malignancies (Table 1). The majority of patients (75.6%) had an ECOG Performance Status of 0-1 at treatment initiation. Most patients received ICIs as first-line therapy (52.4%), while 47.6% received them in the second-line or beyond setting.

Table 1: Patient Demographics and Baseline Characteristics (N=84)

Characteristic	Category	Value
Age (years)	Median (Range)	61 (34–78)
Gender, n (%)	Male	46 (54.8%)
	Female	38 (45.2%)
ECOG PS, n (%)	0-1	63 (75.6%)
	≥2	21 (25.4%)
Line of Therapy, n (%)	First-line	44 (52.4%)
	≥ Second-line	40 (47.6%)
ICI Agent, n (%)	Pembrolizumab	60 (71.4%)
	Nivolumab	19 (22.6%)
	Avelumab	3 (3.6%)
	Atezolizumab	2 (2.4%)

3.2. Incidence and Spectrum of Endocrine irAEs

Endocrine irAEs were documented in 28 patients (33.3%). The spectrum of these toxicities is detailed in Table 2. Thyroid dysfunction was the most frequent manifestation, occurring in 22 patients (26.2%). Among thyroid irAEs, overt or subclinical hypothyroidism was the predominant phenotype (n=19, 22.6%), while destructive thyroiditis presenting with transient hyperthyroidism progressing to hypothyroidism was observed in 3 patients (3.6%).

Other endocrine events included asymptomatic isolated adrenal insufficiency (n=4, 4.8%) and immune-mediated type 1 diabetes mellitus (n=2, 2.4%). No cases of clinical hypophysitis were diagnosed during the observation period.

Table 2: Spectrum and Severity of Endocrine Immune-Related Adverse Events

Endocrine irAE	Total n (%)	CTCAE Grade 1-2, n (%)	CTCAE Grade 3-4, n (%)	Median Time to Onset (weeks)
Any Endocrine irAE	**28 (33.3%)**	**28 (33.3%)**	**0 (0%)**	**8**
Thyroid Dysfunction	22 (26.2%)	22 (26.2%)	0 (0%)	6
- Hypothyroidism	19 (22.6%)	19 (22.6%)	0 (0%)	7
- Hyperthyroidism (Transient)	3 (3.6%)	3 (3.6%)	0 (0%)	4
Adrenal Insufficiency	4 (4.8%)	4 (4.8%)	0 (0%)	12
Type 1 Diabetes Mellitus	2 (2.4%)	2 (2.4%)	0 (0%)	10

3.3. Severity and Clinical Management

A striking finding of this cohort was the absence of high-grade (CTCAE Grade 3-4) endocrinopathies. All 28 documented events were classified as Grade 1 or 2. Consequently, the clinical management relied predominantly on hormonal replacement therapy without the need for high-dose systemic corticosteroids solely for the endocrine event (Table 3).

For the 19 patients developing hypothyroidism, levothyroxine substitution was initiated at a median dose of 50 µg/day. The 3 patients with transient hyperthyroidism were managed with beta-blockers transiently, subsequently requiring levothyroxine upon progression to hypothyroidism. Adrenal insufficiency was managed with oral hydrocortisone replacement (15–20 mg/day).

Crucially, due to the low-grade nature of these toxicities, ICI therapy was permanently discontinued in **none** of the patients experiencing an endocrine irAE. ICI was temporarily held in only 4 patients (4.8%) pending symptomatic stabilization and endocrinological clearance, after which treatment was successfully resumed.

Table 3: Management of Endocrine irAEs and Impact on ICI Therapy

Management Parameter	n (%)
Hormone Replacement Initiated	25 (29.8%)
- Levothyroxine	19 (22.6%)
- Hydrocortisone	4 (4.8%)
- Insulin	2 (2.4%)
High-dose Corticosteroids Required for Endocrine irAE	0 (0%)
Impact on ICI Therapy	
- ICI Continued Uninterrupted	24 (85.7% of irAEs)*
- ICI Temporarily Interrupted	4 (14.3% of irAEs)*
- ICI Permanently Discontinued	0 (0%)

*Percentages calculated based on the 28 patients who experienced an endocrine irAE.

4. Discussion

This study represents the first real-world analysis of endocrine toxicities associated with the newly introduced ICIs in Eastern Algeria. Our findings delineate two critical clinical paradigms: first, the confirmation that endocrine irAEs—

particularly dysthyroidism—are a frequent reality in our population, necessitating structured endocrinological oversight; second, and most notably, the observation that these toxicities manifest with significantly lesser severity compared to established international profiles [Byun et al., 2023; Haanen JBAG et al., 2022].

The overall incidence of thyroid dysfunction (26.2%) in our cohort aligns with the upper bounds of reports from pivotal trials involving pembrolizumab and nivolumab, which typically range from 10% to 30% [Osorio et al., 2015]. However, the strict confinement of all endocrine events to CTCAE Grade 1-2 is a divergent and clinically meaningful finding. In large systematic reviews, Grade 3-4 hypothyroidism or hypophysitis, while rare, are known to occur and often precipitate treatment abandonment or severe morbidity [Fallahi et al., 2020]. The complete absence of fulminant hypophysitis or adrenal crisis in our cohort suggests a potentially favorable pharmacogenomic or immunogenomic profile within the North African demographic, although this hypothesis requires robust prospective validation.

Several factors may explain the milder toxicity profile observed. First, the relatively short follow-up period inherent to the recent introduction of ICIs (late 2024) may preclude the detection of late-onset endocrinopathies, such as hypophysitis, which typically manifests after 9-12 weeks of treatment [Faje et al., 2026]. Second, the implementation of an early, proactive monitoring protocol—driven by the active integration of endocrinologists—may have facilitated the detection of subclinical (Grade 1) hormonal shifts before they could cascade into symptomatic, high-grade organ failure. By initiating low-dose levothyroxine at the earliest sign of TSH elevation, the systemic inflammatory cascade may be mitigated, preventing severe clinical deterioration.

The vocational structure-impact of our model cannot be understated. In many resource-constrained settings, endocrine irAEs are managed reactively by oncologists9. Our model mandated; proactive endocrinological co-management resulted in zero permanent ICI discontinuations due to endocrine toxicity. Given that ICI efficacy is deeply linked to treatment continuation, maintaining dose intensity while safely managing low-grade endocrine sequelae is paramount to maximizing overall survival [Brahmer et al., 2022].

Limitations: This study is limited by its monocentric design, small sample size (N=84), and the observational nature of the data, which limits generalizability. Furthermore, the short observational window since the drugs=drugs' introduction in late 2024 restricts our ability to comment on the long-term chronicity or delayed onset of certain endocrinopathies.

5. Conclusion

In this preliminary real-world experience from Eastern> Eastern Algeria, the integration of PD-1 and PD-L1 inhibitors across multiple oncologic indications demonstrates a reassuringly manageable endocrine safety profile. While endocrine irAEs—predominantly dysthyroidism—are common, their clinical severity is distinctly lower than international benchmarks, allowing for effective hormonal substitution without compromising ICI treatment continuity. These findings strongly advocate for& for the institutionalization of multidisciplinary care frameworks, where endocrinologists are systematically embedded into the oncological surveillance architecture, ensuring prompt, grade-appropriate interventions and optimal patient trajectories.

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