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Consensus

Expert opinions on adrenal complications in immunotherapy

Avis d'experts sur les complications surrénaliennes de l'immunothérapie

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Abstract

Primary adrenal insufficiency during immunotherapy is rare and does not warrant systematic screening during treatment. It should be suspected in case of typical clinical and biological presentation, but also in case of subclinical presentation with impaired general health status and/or hyponatremia. Diagnosis is based on low cortisol levels, measured at any time in case of emergency or else at 8 am, associated to elevated ACTH to rule out pituitary origin. Secondly, anti-21-hydroxylase antibody assay may be performed, with screening for mineralocorticoid deficiency. Imaging is recommended, although not urgent, to screen for “adrenalitis” or adrenal atrophy and rule out differential diagnosis of adrenal metastasis. Primary adrenal insufficiency during immunotherapy is a medical emergency requiring hydrocortisone replacement adapted to the clinical and biological context. Management by an endocrinologist is essential, in order to adapt hydrocortisone and fludrocortisone replacement therapy and to educate both patient and oncologist in hydrocortisone dose adaptation. Current data suggest that treatment needs to be life-long, even after termination of immunotherapy. The present article does not deal with secondary adrenal insufficiency, which is included in the section on “Pituitary toxicity”.

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Keywords: Immunotherapy; CTLA-4; PD-1; PD-L1; Adrenal insufficiency; Hydrocortisone

Recommendations

R1: Diagnosis of primary adrenal insufficiency during anticancer immunotherapy should be considered in case of:

- suggestive acute clinical presentation: asthenia, weight loss, dehydration, hypotension, fever, abdominal pain, nausea, vomiting, diarrhea, cramp and muscle pain;
- subclinical presentation of impaired general health status with hyponatremia;
- or more rarely, isolated hyponatremia or hyperkalemia.

R2: In emergency, in case of suspected acute adrenal insufficiency under immunotherapy, it is recommended:

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- to immediately assay cortisol and if possible ACTH, regardless of time of day;
- then initiate hydrocortisone replacement therapy, without awaiting assay results.

Diagnosis will subsequently be ruled out in case of cortisolemia > 500 nmol/L, regardless of time of day. This threshold should be taken with caution according to the assay kit used.

R3: In non-emergency situations, diagnosis of primary adrenal insufficiency is confirmed by 8-am cortisolemia < 138 nmol/l (5 µg/dL) and elevated plasma ACTH. If 8-am cortisol is between 138 and 500 nmol/L (5–18 µg/dL), a stimulation test such as Synacthen® 250 µg should be performed in second line to screen for “latent” adrenal insufficiency; if the test shows cortisolemia < 500 nmol/L (18 µg/dL), diagnosis of adrenal insufficiency is confirmed. These thresholds should be taken with caution according to the assay kits used.

R4: In case of diagnosis of primary adrenal insufficiency under immunotherapy:

- anti-21-hydroxylase antibodies should be assayed;
- a non-emergency adrenal CT scan should be taken if previous abdominal imaging dates from more than 3 months, to rule out other etiology: adrenal metastasis, infection, bilateral adrenal hemorrhagic necrosis, or granulomatosis.

R5: In case of diagnosis of acute adrenal insufficiency under immunotherapy, 100 mg intravenous, or else intramuscular or subcutaneous, hydrocortisone hemisuccinate is recommended, followed by 24 hours' continuous 100 mg hydrocortisone hemisuccinate with rehydration, as in acute adrenal insufficiency unrelated to immunotherapy. As soon as clinical and biological symptoms improve, oral hydrocortisone relay at 60 mg per 24 hr should be rapidly initiated, reduced to 15–30 mg per 24 hr if there is no acute disease. Fludrocortisone 50 µg/day may be initiated and secondarily adapted by the endocrinologist.

R6: In case of acute adrenal insufficiency, immunotherapy may be postponed but should never be definitively contraindicated. It may be reintroduced at usual doses as soon as hydrocortisone replacement is effective and the patient is clinically and biologically stable (blood ionogram).

R7: In case of known primary adrenal insufficiency in a patient undergoing immunotherapy, daily hydrocortisone dose is 15–30 mg/day, to be adapted to clinical and biological presentation and general health status. At such doses, replacement has no immunosuppressive effect. Fludrocortisone replacement is adapted according to blood pressure and to blood potassium and possibly renin levels. The patient should be followed by an endocrinologist for long-term monitoring and therapeutic education on prevention of acute episodes. How to adapt hydrocortisone therapy in acute events should also be explained to the patient's oncologist.

R8: Given the rarity of primary adrenal insufficiency under immunotherapy, there is no need for systematic screening before or during immunotherapy, except in case of alarm signs.

R9: Current data suggest that replacement therapy should be life-long.

1. Epidemiology

Among the numerous endocrine side effects of immunotherapy, primary adrenal insufficiency (PAI) is not frequent. Oncologic series reported adrenal insufficiency rates of less than 1% in monotherapy and 4–8% in associations [1–3]. However, the primary or secondary nature of the etiology was not specified, and the figures are to be taken with caution. There are to date only 6 cases sufficiently well documented in hormonal terms to be able to attest to PAI rather than the more frequently reported corticotroph deficiency. It cannot be ruled out that corticotroph deficiency secondary to hypophysitis or corticosteroid intake is mistaken for PAI and reported as such in oncologic trials (Table 1) [4–15]. Systematic ACTH assay in oncology would allow better estimates of the relative frequency of PAI and corticotroph deficiency (detailed in the section on the pituitary side-effects of immunotherapy) secondary to immunotherapy.

In oncologic series, PAI rates have not been shown to differ according to molecule, given the small numbers involved. The larger number of cases associated with anti-CTLA4 (ipilimumab) [16] than with anti-PD1s (pembrolizumab, nivolumab) [16] may be due to the larger number of reports for ipilimumab compared to other immunomodulators. Prevalence of PAI does not seem to vary significantly according to type of cancer: the 6 published observations mainly concerned melanoma, which may be due to there being more reports of immunotherapy for this cancer. Finally, published data suggest dose-dependence, PAI being reported for ipilimumab > 5 mg/kg [5] or for high-dose pembrolizumab [6].

According to present data, the molecules associated with proven immunotherapy-related PAI are ipilimumab, pembrolizumab and nivolumab.

Table 1
 Main clinical trials in adrenal insufficiency.

	Type of trial	Molecule(s) Dose	Primary tumor	Number of cases (%)	Details	Hypophysitis/ Hyponatremia
Yang et al., 2007 [4]	Phase I	Ipilimumab 3 mg/kg	mRCC	1/61 (1.6)	Single adrenal metastasis	2 hypophysites, including 1 with ACTH elevation
Weber et al., 2008 [5]	Phase I/II	Ipilimumab 20 mg/kg × 1 or 5 mg/kg × 4 or 10 mg/kg × 4	Melanoma	1/88 (1)	NR	NR
Hersh et al., 2009 [6]	Phase II	Ipilimumab 3 mg/kg × 4	Melanoma	1/74 (1.3)	1 grade 2	NR
Hodi et al., 2010 [7]	Phase III	Ipilimumab 3 mg/kg × 4	Melanoma	5/511 (1)	3 grade 1–2 2 grade 3	4 hypophysites 6 pituitary insufficiencies
Madan et al., 2012 [8]	Phase I	Ipilimumab 5 or 10 mg/kg	mCRPC	3/30 (10)	1 grade 2 2 grade 3	1 hyponatremia
Wolchok et al., 2013 [9]	Phase I	Nivolumab + Ipilimumab Dose escalation	Melanoma	3/86 (3.4)	2 grade 1–2 1 grade 3–4	3 hypophysites
Ryder et al., 2014 [10]	Single-center retrospective	Ipilimumab Variable	All	1/256 (0.3)	Bilateral adrenal metastasis	–
Kwon et al., 2014 [11]	Phase III	Ipilimumab 10 mg/kg × 4	mCRPC	6/393 (2)	4 grade 1–2 2 grade 3	NR
Postow et al., 2015 [12]	Phase I	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Melanoma	Ipi + nivo: 6/94 (6.4) Ipi only: 2/46 (2.2)	5 grades 1–2/1 grades 3–4 1 grade 1–2/1 grades 3–4	10 hypophysites 3 hypophysites
Rizvi et al., 2015 [13]	Phase II	Nivolumab 3 mg/kg/2 W	NSCLC	1/117 (1)	1 grade 3–4 1 stop	1 hyponatremia
Herbst et al., 2016 [14]	Phase II/III	Pembrolizumab 2 or 10 mg/kg/3 W	NSCLC	2 mg/kg: 2/339 (1) 10 mg/kg: 3/343 (1)	4 grades 1–2 1 grade 3–5	2 hypophysites
Gulley et al., 2017 [15]	Phase I	Avelumab 10 mg/kg/2 W	NSCLC	2/184 (1)	2 grades 1–2 1 stop	1 grade 3 hyponatremia

mRCC: metastatic renal cell carcinoma; NR: not reported; mCRPC: metastatic castration-resistant prostate cancer; NSCLC: non-small-cell lung cancer.

2. Pathophysiological mechanisms

Pathophysiological mechanisms are unknown. Anti-adrenal antibodies were detected in 2 patients [17,18]. Certain reports mention a morphologic aspect they refer to as “adrenalitis” (adrenal inflammation) [19,20]. FDG-PET scan finds uniform hypermetabolism in both glands [19,21]. Adrenal atrophy, similar to that found in Addison’s disease, was also reported in 1 patient [17]. The definitive nature of the adrenal insufficiency in these clinical cases is compatible with adrenal destruction by an autoimmune mechanism induced by immunotherapy. In oncologic series of PAI, screening for anti-adrenal antibodies and morphologic aspect were not reported.

3. Diagnosis

3.1. Positive diagnosis

Immunotherapy-induced PAI shows no clinical specificities. Two clinical situations are reported: typical acute presentation [18] or a more progressive subacute presentation that is more difficult to diagnose in this context of potentially toxic anticancer treatment [21]. Median time to onset is highly variable [3]: 4.3 months for nivolumab, 2.5 months for avelumab, and < 5 months in 4 case reports (Table 2). Onset may also be late after termination of immunotherapy, as reported for pembrolizumab [18]. PAI may be associated with other endocrine toxicity: 2 patients

Table 2
Case reports of primary adrenal insufficiency under immunotherapy.

	Bacanovic et al. [19]	Min et al. [20]	Trainer et al. [21]	Paepegaey et al. [18]	17Hescot et al.
Drug	Ipilimumab	Ipilimumab	Nivolumab	Pembrolizumab	Pembrolizumab
Indication	Choroid melanoma	Melanoma	Melanoma	Choroid melanoma	Cervical squamous cell carcinoma
Age at diagnosis	79 years	56 years	45 years	55 years	33 years
Clinical and biological presentation	Asymptomatic	Asthenia and headache (concomitant hypophysitis)	Asthenia Isolated hyponatremia	Adrenal crisis Hyponatremia, acute renal failure	Adrenal crisis Hyponatremia, acute renal failure
Hormonal presentation	Not reported	Low corticotropin Low cortisol No response of cortisol and aldosterone to cosyntropin	Low cortisol, no response to Synacthen High corticotropin High renin, low aldosterone	Low cortisol, no response to Synacthen High corticotropin High renin, low aldosterone 21-hydroxylase antibodies positive	Low cortisol, no response to Synacthen High corticotropin High renin, low aldosterone 21-hydroxylase antibodies positive
Time between treatment initiation and AI	3 months 1 month after treatment withdrawal	4 months	2 months	10 months 1 month after treatment withdrawal	5 months
Associated toxicity	Not reported	Concomitant hypophysitis	Not reported	Previous thyroiditis	Previous thyroiditis
Concomitant RECIST evaluation	Not reported	Not reported	Complete response	Not reported	Partial response
Follow-up	Not reported	Not reported	1 year: persistent AI	Not reported	1 year: persistent AI

presented associated thyroiditis [17,18] and 1 hypophysitis [20]. In all cases, prior intake of corticosteroids (potentially causing pre-existing iatrogenic corticotroph deficiency) and any trigger factor should be screened for.

R1: Diagnosis of primary adrenal insufficiency during anti-cancer immunotherapy should be considered in case of:

- suggestive acute clinical presentation: asthenia, weight loss, dehydration, hypotension, fever, abdominal pain, nausea, vomiting, diarrhea, cramp and muscle pain;
- subclinical presentation of impaired general health status with hyponatremia;
- or more rarely, isolated hyponatremia or hyperkalemia.

In acute presentations, clinical signs appear within hours or days, and may be associated with a trigger such as infection. Patients may show asthenia, unusual fatigability, anorexia, nausea or vomiting, diarrhea, sometimes abdominal pain (generally diffuse), orthostatic or unusual hypotension, tachycardia, signs of dehydration, moderate hyperthermia, and/or diffuse pains (cramps). Signs are comparable to those of non-iatrogenic PAI. Severity signs include hypotension, tachycardia, consciousness disorder, and neurologic disorder (confusion, agitation). Emergency analyses should at least include cortisolemia (at whatever time of day) before rapidly initiating hydrocortisone without awaiting results [22]. Cortisolemia > 500 nmol/L at whatever time of day rules out the diagnosis retrospectively.

R2: In emergency, in case of suspected acute adrenal insufficiency under immunotherapy, it is recommended:

- to immediately assay cortisol and if possible ACTH, regardless of time of day;
- then initiate hydrocortisone replacement therapy, without awaiting assay results.

Diagnosis will subsequently be ruled out in case of cortisolemia > 500 nmol/L, regardless of time of day. This threshold should be taken with caution according to the assay kit used.

In subclinical presentations with very progressive onset of adrenal insufficiency, clinical signs may be non-specific, with simple impaired general health, weight loss, isolated diarrhea or confusion, and diagnosis is more difficult. Biologically, PAI is usually associated with hyponatremia (sodium loss due to mineralocorticoid deficit and inappropriate ADH secretion), hyperkalemia, low glycemia, metabolic acidosis and functional kidney failure related to hypovolemia. Normocytic normochromic anemia, lymphocytosis and hypereosinophilia may also be found. Some subclinical presentations comprise only isolated hyponatremia. When adrenal insufficiency is suspected without any clinical or biological emergency, 8-am cortisolemia is indicated in first line [22]. If 8-am cortisol is low (below the laboratory's normal value, generally < 138 nmol/L (5 µg/dL)), adrenal insufficiency is diagnosed; for 138–500 nmol/L (5–18 µg/dL), assessment should be completed by dynamic cortisol secretion stimulation testing, for example by Synacthen® 250 µg. ACTH > 100 pg/mL with normal cortisolemia is also highly suggestive. Plasma aldosterone and renin assay in second line screen for mineralocorticoid deficit.

R 3: In non-emergency situations, diagnosis of primary adrenal insufficiency is confirmed by 8-am cortisolemia < 138

nmol/L (5 µg/dL) and elevated plasma ACTH. If 8-am cortisol is between 138 and 500 nmol/L (5–18 µg/dL), a stimulation test such as Synacthen® 250 µg should be performed in second line to screen for “latent” adrenal insufficiency; if the test shows cortisolemia < 500 nmol/L (18 µg/dL), diagnosis of adrenal insufficiency is confirmed. These thresholds should be taken with caution according to the assay kits used.

3.2. Etiologic diagnosis

The primary or secondary etiology of adrenal insufficiency is determined on ACTH assay. In PAI, anti-21-hydroxylase antibody assay should be performed to screen for autoimmune origin. If abdominal imaging in cancer monitoring dates back more than 3 months, adrenal CT should be performed to screen for adrenal morphologic abnormality (aspect of “adrenality” or adrenal atrophy) and to rule out differential diagnosis of bilateral adrenal metastasis or of tuberculosis.

R4: In case of diagnosis of primary adrenal insufficiency under immunotherapy:

- anti-21-hydroxylase antibodies should be assayed;
- a non-emergency adrenal CT scan should be taken if previous abdominal imaging dates from more than 3 months, to rule out other etiology: adrenal metastasis, infection, bilateral adrenal hemorrhagic necrosis, or granulomatosis.

4. Treatment

4.1. Treatment of acute adrenal insufficiency

Acute adrenal insufficiency is a medical emergency. Hydrocortisone should be initiated without awaiting endocrinologic opinion or emergency cortisolemia results. Treatment consists in intravenous, or else intramuscular or subcutaneous, hydrocortisone hemisuccinate 100 mg injection associated with intravenous rehydration (plus glucose serum in case of associated hypoglycemia) and 100 mg continuous intravenous hydrocortisone hemisuccinate for the following 24 hours [23]. Once the patient shows stabilization and then improvement, the dose can be progressively reduced and oral relay initiated. Any trigger factor (e.g., viral or bacterial infection) should be treated.

R5: In case of diagnosis of acute adrenal insufficiency under immunotherapy, 100 mg intravenous, or else intramuscular or subcutaneous, hydrocortisone hemisuccinate is recommended, followed by 24 hours’ continuous 100 mg hydrocortisone hemisuccinate with rehydration, as in acute adrenal insufficiency unrelated to immunotherapy. As soon as clinical and biological symptoms improve, oral hydrocortisone relay at 60 mg per 24 hr should be rapidly initiated, reduced to 15–30 mg per 24 hr if there is no acute pathology. Fludrocortisone 50 µg/day may be initiated and secondarily adapted by the endocrinologist.

R6: In case of acute adrenal insufficiency, immunotherapy may be postponed but should never be definitively contraindicated. It may be reintroduced at usual doses as soon as

hydrocortisone replacement is effective and the patient is clinically and biologically stable (blood ionogram).

4.2. Treatment of chronic adrenal insufficiency

Long-course treatment of PAI does not differ from that usually recommended for Addison’s disease [24]. It comprises hydrocortisone (necessary dose, 9.9 ± 2.2 mg/m²/day: i.e., 20–30 mg in 2 or 3 doses per day) and fludrocortisone (mean, 100 µg per day). The patient should receive therapeutic education. The relevant specificity is the diathesis: oncologic comorbidity and risk of anticancer drug toxicity. Baseline hydrocortisone requirements may be higher than in Addison’s disease without associated comorbidity, and are to be estimated on a case-by-case basis. Hydrocortisone and fludrocortisone doses are to be adapted according to clinical status (general health status, blood pressure, nausea, vomiting, diarrhea and abdominal pain) and to natremia, blood potassium and kidney function. Risk of acute decompensation is especially high in these patients, who are at greater risk of infection, diarrhea, surgery or other “medical stress” situations, and in whom diagnosis of acute adrenal insufficiency is hindered by the poor specificity of symptoms. Hydrocortisone treatment should be life-long, and patient education by an endocrinologist is necessary, even in oncologic contexts and whatever the patient’s life expectancy. Oncology team training in the treatment of adrenal insufficiency is indispensable to prevent acute insufficiency, especially in case of vomiting. DHEA replacement therapy does not seem to need to be systematic, and is to be discussed with the endocrinologist. Recommendations for the prevention of acute adrenal insufficiency are similar to those in all cases of adrenal insufficiency.

R7: In case of known primary adrenal insufficiency in a patient undergoing immunotherapy, daily hydrocortisone dose is 15–30 mg/day, to be adapted to clinical and biological presentation and general health status. At such doses, replacement has no immunosuppressive effect. Fludrocortisone replacement is adapted according to blood pressure and to blood potassium and possibly renin levels. The patient should be followed by an endocrinologist for long-term monitoring and therapeutic education on prevention of acute episodes. How to adapt hydrocortisone therapy in acute events should also be explained to the patient’s oncologist.

5. Monitoring

5.1. Before and during immunotherapy

As PAI is rare, data are insufficient to recommend systematic 8-am cortisolemia before or during immunotherapy. Systematic anti-21-hydroxylase antibody assay ahead of immunotherapy is not indicated, given the rarity of PAI. The few published reports suggest that immune-induced PAI may occur during immunotherapy or after termination.

R8: Given the rarity of primary adrenal insufficiency under immunotherapy, there is no need for systematic screening before or during immunotherapy, except in case of alarm signs.

5.2. After diagnosis of PAI

PAI seems to be definitive, according to the data for the few cases reported, with a maximum 1 year's follow-up [21].

R9: Current data suggest that replacement therapy should be life-long.

Disclosure of interest

The authors declare that they have no competing interest.

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