Annals of Clinical Case Reports

Case Report
Published: 09 Oct, 2023

Infections in Patients with Addison's Disease: Considerations in Primary Care

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Abstract

Patients with Addison's disease may present to primary care with infection; this can be a high-risk situation due to the risk of an Addisonian crisis. A careful history and examination searching for a potential infective source and assessing for 'red flags' such as fevers, abdominal pain, and vomiting, are crucial. The characteristic electrolyte changes in Addisonian crisis are hyponatremia and hyperkalemia. Hypercalcemia is also often present, as is eosinophilia.

Emergency management if crisis is suspected includes a rapid ABCDE assessment, intramuscular steroid injection, and transfer to the emergency department. Less urgent management would likely include guideline-directed antibiotics and an increase in steroid dose ('sick day rules'). Follow-up should involve discussion of wellbeing, a reminder to increase steroid dosage to support the stress response, a reminder on emergency injections, and a medication review. Endocrine referral should be considered, and follow-up blood tests may help confirm resolution of infection. Psychosocial support is also important, as are preventive measures such as influenza vaccination.

Introduction

Addison's disease is a chronic condition characterized by primary adrenal insufficiency, due to autoimmune or secondary causes. Periods of increased stress, such as infections, can be dangerous in these patients due to the risk of an Addisonian crisis [1].

In primary care, it is crucial to identify the signs of Addisonian crisis; this report summarizes the example of an Addison's patient suffering from an acute infection who was managed appropriately, and discusses the key features on history and examination, classic investigation findings, emergency management, and follow-up including psychosocial support.

Case Presentation

A 57-year-old lady with Addison's disease, hypothyroidism, partial hypopituitarism, and type 2 diabetes mellitus presented to her GP with a week of fever and 4 days of productive cough that had failed to respond to amoxicillin treatment initiated after a telephone appointment 3 days prior. The patient was found to be mildly tachycardic (102) and had bilateral basal crackles. The GP had commenced co-amoxiclav (500 mg/125 mg tablets TDS) and confirmed that the patient had increased her steroid dose to support the stress response. Crucially, safety-netting instructions were provided.

The patient's symptoms worsened over the following 3 days; she urgently consulted the GP with pronounced symptoms of dyspnea, chest pain, and worsening cough. Hence, she was advised to go to A&E immediately.

Blood tests in hospital excluded an Addisonian crisis but showed leukocytosis, and a chest X-ray confirmed lower lobe pneumonia. The patient required emergency hospital admission for stabilization, IV fluids, and antibiotics.

Discussion

The vignette highlights the importance of prompt diagnosis and swiftly excluding Addisonian crisis in Addison's patients who present with an infection. Our patient had a severe chest infection requiring hospital admission. Without the appropriate steps taken in primary care (Table 1), the patient may have progressed to an Addisonian crisis.

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Received Date: *19 Sep 2023*
Accepted Date: *05 Oct 2023*
Published Date: *09 Oct 2023*

Citation:
S Kapadia, A Saad. Infections in Patients with Addison's Disease: Considerations in Primary Care. Ann Clin Case Rep. 2023; 8: 2493.
ISSN: 2474-1655.

Table 1: Suggested steps in primary care during and after infection in Addison's patients.

During	After
✓ History & examination with focus on red flags + antibiotics if indicated	✓ Appointment to explore general wellbeing, self-care, and safety
✓ Confirm patient has increased steroid dosage to support the stress response	✓ Medication reconciliation
✓ Safety-net with low threshold for A&E	✓ Blood tests esp. endocrine, and endocrine follow-up
✓ Availability of urgent review if needed	✓ Psychological support

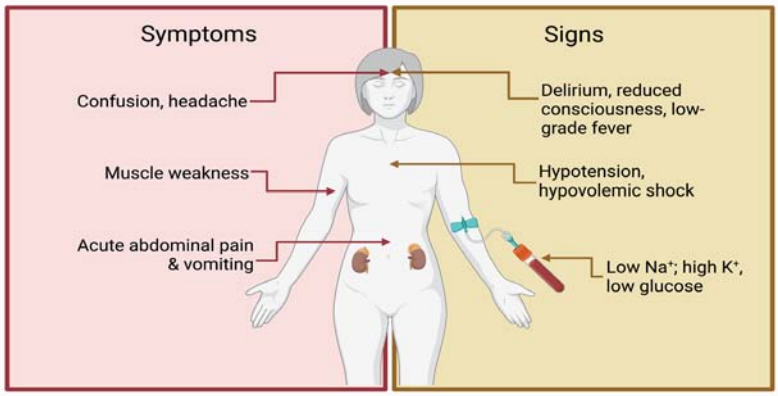

Figure 1: Original illustration to show 'red-flag' symptoms and signs of Addisonian crisis [6].

There appears to be a bidirectional relationship between endocrine conditions and infection [2] - severe infections precipitate endocrine exacerbations such as Addisonian crisis, and conversely endocrine conditions may predispose to infection [2-4]. A recent UK study showed that patients with Addison's disease were more likely to develop infection than the general population [3].

A high index of suspicion for infection must be maintained in Addison's patients, and as such, a more severe infection should be anticipated. The potential 'blunting' of sympathetic responses with hypoadrenalism [5] as well as the potential 'masking' of infection due to chronic Addison's symptoms such as fatigue, malaise, and depression, makes this even more crucial. However, less-common differentials such as rheumatological conditions, heat stroke, hyperosmolar hyperglycemic state, thyroid storm, cancers, acute surgical abdomen, and medication adverse effects should also be considered.

A thorough history to assess the likelihood and source of infection as well as the risk of adrenal crisis is essential. This should include onset, duration, and progression of symptoms and a detailed review of compliance with steroid therapy. In patients with ongoing symptoms, exacerbations should be looked out for (such as the dyspnea and worsened cough in this case). Red flag symptoms for adrenal crisis (Figure 1) should be specifically asked. These may include low-grade subjective fevers, gastrointestinal symptoms such as acute abdominal pain and vomiting, and neurological symptoms such as headache, dizziness, and weakness [4]. Hypoglycemic symptoms may also be seen, typically in children [4]. Enquiry about gastrointestinal symptoms is particularly important; not only because Addisonian crises have several abdominal features, but also because gastroenterological infections are the most common trigger of Addisonian crisis [1]. A review of fluid intake and toileting patterns is similarly relevant. If the initial appointment is by telephone, a low threshold should be maintained to see the patient face-to-face or send them to A&E / arrange an urgent medical admission (which was critical in this case).

When the patient is seen face-to-face, examination should involve a search for the infective source, an assessment of the severity of the infection, and a search for red flags (Figure 1) such as volume depletion, hypotension, tachycardia, and delayed capillary refill (hypovolemic shock is a cardinal sign of Addisonian crisis).

A mental status examination is also useful as delirium or reduced consciousness may be present [6]. A full blood count, inflammatory markers, and U&Es may help characterize the infection and show warning signs of an Addisonian crisis. The characteristic electrolyte changes in Addisonian crisis are hyponatremia and hyperkalemia. Hypercalcemia is also often present, as is eosinophilia. In theory, interpretation of the leukocyte count may be confounded as steroids promote neutrophil demargination from the blood vessel walls into the bloodstream, whilst lowering lymphocyte counts [7]. However, in practice, high white cell count is likely a sound indicator of infection in patients on stable steroid regimens. Finally, as a safety net, patients should be urgently sent to hospital for stabilization and a medical opinion if symptoms worsen or red flags develop.

If adrenal crisis is suspected at any point during evaluation, or if the infection is severe (vomiting, persistent diarrhea, or other), emergency management is recommended with a rapid ABCDE assessment, ideally with administration of an intramuscular steroid injection, and ambulance transfer to the emergency department [6]. In adults not requiring emergency transfer, guideline-directed antibiotics, and an increase in steroid dose (which the GP checked in this case) to support the stress response are crucial. NICE suggests doubling the dose for 'moderate' illness (fever >37.5°C, requiring bedrest, or requiring antibiotics), as in our patient [6]. Severe nausea requires 20 mg PO hydrocortisone and oral rehydration [6]. For COVID-19 and pediatric patients, NICE recommends urgent specialist advice [6].

After a severe infection (with or without hospital admission) in an Addison's patient, there are several considerations in primary care regarding follow-up (Table 1). A face-to-face appointment is ideal, with discussion of wellbeing, a reminder to increase steroid dosage to

support the stress response, a reminder on emergency injections, and a medication review [6], particularly for patients admitted to hospital (in our case, the patient's asthma medication was stopped in hospital, worsening her symptoms). A referral for specialist endocrine review for medication optimization should be considered. Follow-up blood tests may include a full blood count and inflammatory markers to help confirm resolution of infection, as well as endocrine tests for co-morbid conditions (hypothyroidism in our patient's case).

Psychosocial management should not be overlooked; severe infections, particularly if the patient suffered a near-miss Addisonian crisis, can take a toll on patients' mental health. Such events can cause low self-esteem, anxiety, and can cause patients to become discouraged which may impact compliance with steroid therapy, constituting a vicious cycle. Psychiatric co-morbidities, which are often seen in Addison's [8], may be exacerbated, particularly depression. A brief screen for low mood, anergia, anhedonia, and thoughts of self-harm could be valuable. Indeed, the patient in our vignette had co-morbid depression.

Prevention is also key, such as ensuring the patient has received influenza vaccination and reviewing diet and nutrition.

Conclusion

Infections in Addison's patients can be severe and may precipitate Addisonian crisis if allowed to progress. Effective primary care management in such cases requires alertness for red flags, careful safety netting, enabling urgent review if required, keeping a low threshold for advising A&E, and holistic follow-up to minimize impact and prevent recurrence.

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