

# Fatal Rotavirus Infection in a 4-Year-Old with Unsuspected Autoimmune Adrenal Insufficiency

Alison Krywaczyk, Elizabeth A. Bundock

## ABSTRACT

The diagnosis of adrenal insufficiency is often delayed, as the presenting symptoms of fatigue, abdominal pain, and anorexia are vague and nonspecific. However, timely diagnosis and treatment with replacement steroids are needed to prevent fatal adrenal crisis. While the most common cause of primary adrenal insufficiency in childhood is congenital adrenal hyperplasia, a significant minority (13-23%) is caused by autoimmune destruction of the gland. We present a case of a 4-year-old, previously healthy child who had a one-day history of nausea and vomiting, and was found unresponsive by her caretaker. Despite emergency rescue and transport to the hospital, she was pronounced dead. At autopsy, the adrenal glands were atrophied. Histologic examination revealed lymphocytic infiltration of the adrenal glands consistent with autoimmune adrenal insufficiency. Fecal viral antigen testing was positive for rotavirus. The cause of death was determined to be adrenal crisis in the setting of rotavirus gastroenteritis due to adrenal insufficiency (Addison disease). *Acad Forensic Pathol.* 2017 7(1): 130-135

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## AUTHORS

**Alison Krywaczyk MD**, University of Vermont Medical Center

*Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.*

**Elizabeth A. Bundock MD PhD**, Office of Chief Medical Examiner - Vermont State Department of Health

*Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, general administrative support, writing assistance and/or technical editing.*

## CORRESPONDENCE

Alison Krywaczyk MD, EP2 111 Colchester Ave., Burlington VT 05401, Alison.Krywaczyk@uvmhealth.org

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## STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

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## KEYWORDS

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## INTRODUCTION

Adrenal insufficiency (AI) is an uncommon disease in adults and even more rare in children (1). However, prompt recognition and diagnosis of AI is needed to begin treatment and prevent a potentially fatal adrenal crisis (2). Adrenal insufficiency can be subdivided into either primary or secondary/tertiary. In primary AI, the production of mineralocorticoids and glucocorticoids is impaired due to destruction of the adrenal cortex. In contrast, secondary or tertiary AI results from diseases affecting the pituitary or hypothalamus. In these, the production of mineralocorticoids is usually intact because the renin-angiotensin-aldosterone pathway still functions; however, production of corticosteroids is impaired due to impaired production of adrenocorticotrophic hormone (ACTH) (3). Secondary AI is most common form of AI and is typically due to the abrupt withdrawal of pharmacologic treatment with corticosteroids (4).

The term “Addison disease” is nonspecific, referring to any chronic form of primary AI (2). While autoimmune adrenalitis (also known as idiopathic Addison disease) is the most common cause of primary AI in adults in developed countries, the most common cause of primary AI in children is congenital adrenal hyperplasia (CAH). However, a significant minority (13 to 23%) of primary AI in children is due to autoimmune adrenalitis. Unlike autoimmune AI, CAH most commonly presents in the neonatal period (1, 5) and it has been proposed that autoimmune AI is the most common cause of primary AI presenting after the neonatal period (6). We present a case report of a 4-year-old child with subclinical autoimmune adrenalitis who experienced a fatal adrenal crisis precipitated by rotavirus infection.

## CASE REPORT

A 4-year-old previously healthy child was found unresponsive by her caregiver after a one- to two-day history of an illness characterized by nausea and vomiting. Emergency medical services were called and she was transported to the hospital where she was pronounced dead after attempted resuscitation.

Autopsy revealed an underweight, otherwise well-developed 4-year-old. Weight-for-stature was 3rd percentile, while weight-for-age was 25th percentile. No areas of hyperpigmentation on the skin were observed. The right and left adrenal glands were markedly atrophic, weighing less than 1 g each (expected combined weight of 6 g). The pituitary, pancreas, and thyroid glands were grossly unremarkable.

Microscopic evaluation of the adrenals showed lymphoplasmacytic inflammation (**Image 1**) consisting predominantly of T cells with a slight predominance of CD8 to CD4 positive cells. Focal follicle formation by CD20 positive B cells was also observed (**Image 2**).

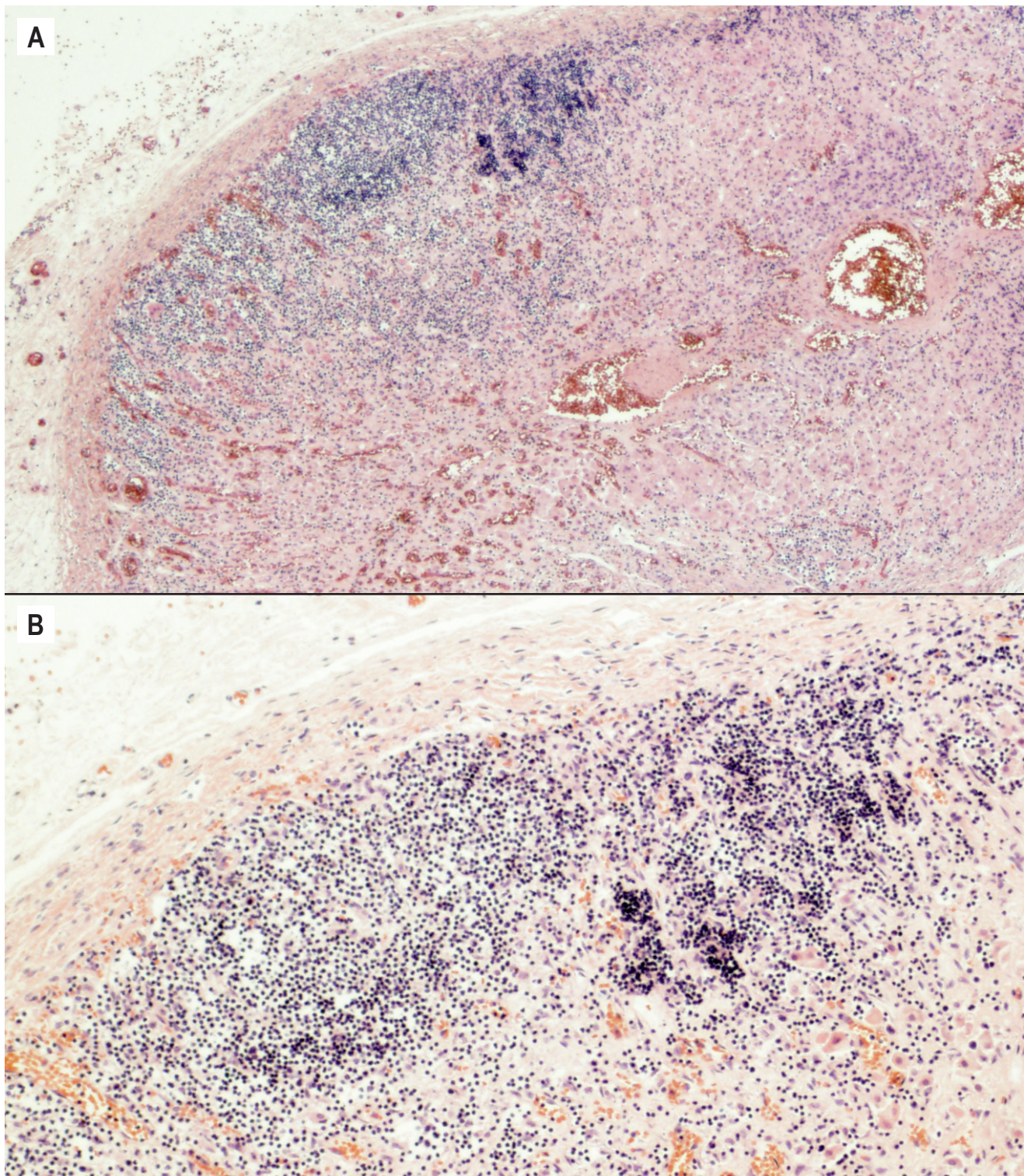
The contents of the small intestine were mucoid and bilious. Microscopic examination showed superficial necrosis of the mucosa, with increased lymphocytes in the lamina propria. The pancreas was microscopically unremarkable.

Postmortem serum cortisol was 1  $\mu\text{g/dL}$  (reference range, 3–22  $\mu\text{g/dL}$ ). Fecal viral antigen testing detected rotavirus. Vitreous sodium was 136 mmol/L and vitreous glucose was <35 mg/dL. Hemoglobin A1C was 5.2%.

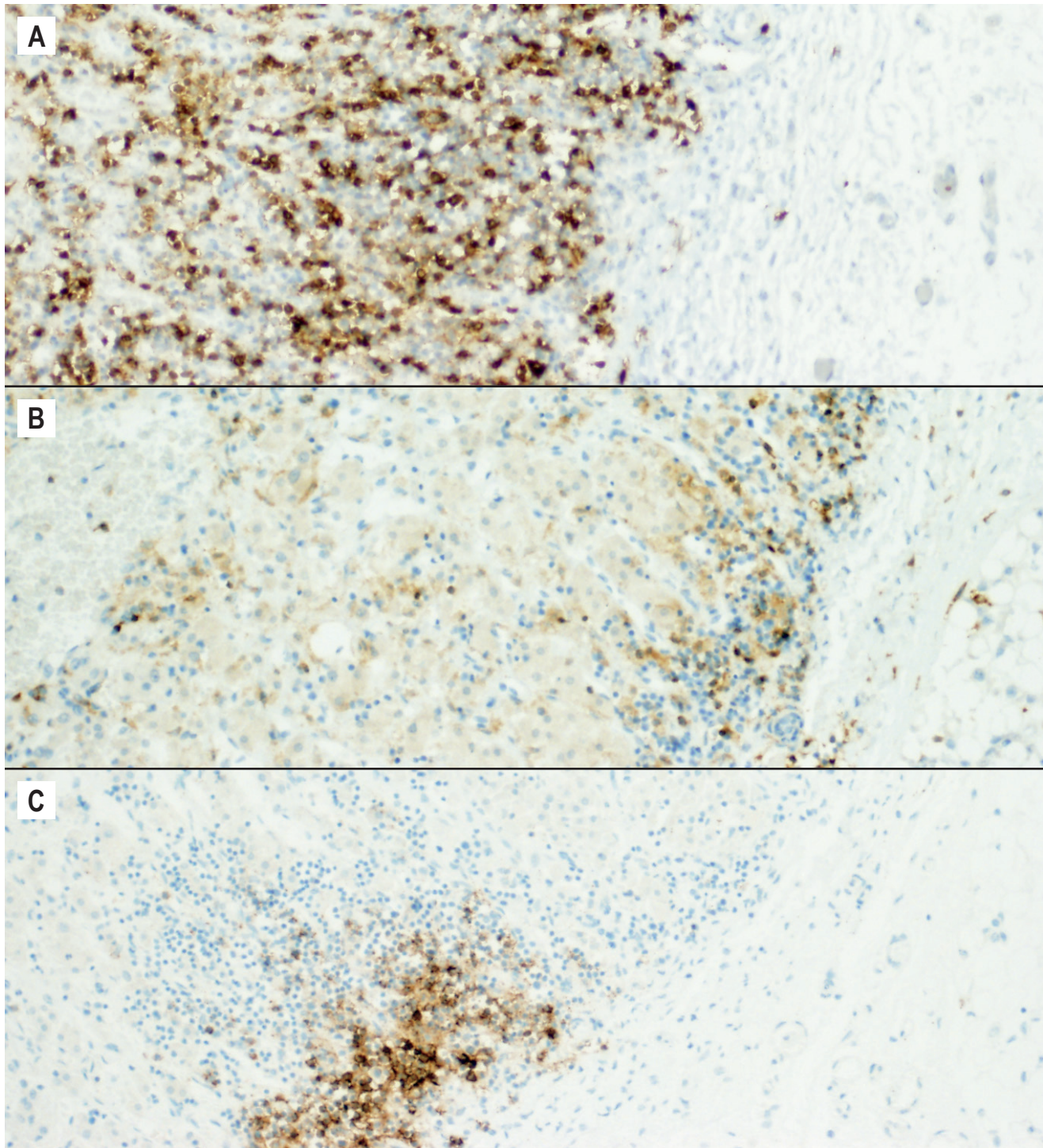
The gross and histologic features of the adrenal glands, combined with the low serum cortisol and clinical history, are essentially diagnostic of an adrenal crisis due to autoimmune adrenalitis. The cause of death was determined to be adrenal crisis in the setting of rotavirus gastroenteritis due to adrenal insufficiency (Addison disease).

## DISCUSSION

Although timely diagnosis of adrenal insufficiency is needed to initiate treatment and prevent adrenal crisis, it is often delayed due to the nonspecific nature of the presenting symptoms. Initial symptoms and signs may include nausea and vomiting, behavioral changes, poor weight gain, hypoglycemia, weakness, and hypotension (1, 6). Further confounding the issue is the inconsistent presence of specific findings to suggest primary AI. Skin hyperpigmentation, often thought of



**Image 1:** Photomicrograph of the left adrenal gland demonstrating diffuse infiltration and destruction of the adrenal cortex by lymphocytes and plasma cells. **A)** H&E, x40 **B)** H&E, x100.



**Image 2:** Immunohistochemistry of left adrenal gland demonstrating proportion of CD8+ T cells, CD4+ T cells, and B cells. This series of photomicrographs depicts the results of immunohistochemical staining of the left adrenal glands for **A)** CD8 (x100), **B)** CD4 (x100), and **C)** CD20 (x100). This demonstrates a slight predominance of CD8+ to CD4+ T cells, and highlights scattered follicle formation by B cells.

as a classic sign of primary AI, may be absent in up to one third of patients (and was absent in the presented case). Hyperkalemia is also absent in up to 50% of children and usually only mild when present (1, 7). One study that examined children with non-CAH primary AI found a delay in diagnosis of up to 0.5-5 years, and 25% of these children presented in frank adrenal crisis (8). Adrenal crises can also be precipitated by infection, as in the case presented here, surgery, or trauma, as these physiologic stresses increase demand for cortisol and the adrenal glands are unable to respond appropriately (2).

At autopsy, the adrenal glands in autoimmune AI can be normal-sized, atrophic, or nearly unidentifiable. Other common causes of primary AI in children include traumatic adrenal hemorrhage, adrenal hemorrhage due to infection (i.e., Waterhouse-Friderichsen Syndrome), thrombosis from antiphospholipid antibody syndrome, direct infection of the gland (e.g., tuberculosis), X-linked adrenoleukodystrophy, and other congenital syndromes (7, 13). However, these etiologies do not cause atrophy of the adrenals. Histologic exam of the adrenal cortex in autoimmune AI typically shows a lymphocyte-predominant infiltrate with associated follicle formation and fibrosis. In the late stages of disease, the glands may be predominantly fibrotic with only minimal inflammation (6, 9).

Postmortem laboratory studies supportive of primary AI include a depressed serum cortisol concentration, often  $<3 \mu\text{g/dL}$ . The cut-off for “low” cortisol may even be raised to  $20 \mu\text{g/dL}$  in patients who are critically ill, and should be demonstrating elevated cortisol as a stress response. Clearly, there is room for uncertainty; some authors suggest a cutoff of  $<5 \mu\text{g/dL}$  to increase sensitivity, and additionally, cortisol concentrations are known to fluctuate during the day (2, 10). The concentrations measured, therefore, needs to be interpreted in the clinical context in order to understand its significance. Serum cortisol has been described to be stable at least up to 18-20 hours post-mortem, and possibly up until the onset of recognizable decomposition (2, 10, 11). In the case presented, the postmortem interval between death and autopsy was only 18 hours, so this should not significantly

confound the interpretation of the decreased cortisol concentration.

While hyponatremia can be detected in the vitreous fluid seen due to loss of aldosterone, vitreous sodium does decrease with increasing decomposition and this must be considered. Hypoglycemia may be detected in the vitreous fluid as well, due to the loss of cortisol, but vitreous glucose is also known to drop after death and so a low value must be interpreted with some scrutiny. Evaluating hyperkalemia in vitreous fluid is entirely unreliable, as potassium begins to increase immediately and unpredictably after death. If antemortem samples are available for testing, then these electrolyte derangements could be confirmed (2, 12). Adrenocorticotropic hormone concentrations and plasma renin activity can also be measured on antemortem samples, and should both be elevated in primary AI (7). In the case presented, no antemortem samples were available for testing.

The detection of auto-antibodies against 21-hydroxylase is specific for autoimmune AI, and can be done on postmortem samples (2).

Other associated endocrinopathies need to be considered when investigating a potential case of autoimmune AI. Autoimmune AI can occur in children in isolation, or may be part of the Autoimmune polyglandular syndromes (types 1, 2, or 4). Autoimmune polyglandular syndromes Type 1 is defined by a germline mutation in the *AIRE-1* gene, and presents with adrenal insufficiency, hypoparathyroidism, and mucocutaneous candidiasis. Autoimmune polyglandular syndrome Type 2 has no single specific mutation, but is defined as adrenal insufficiency with immune-mediated diabetes mellitus and autoimmune thyroiditis. Type 4 is simply any constellation of autoimmune diseases that doesn't fit into the other categories (6). In this patient, there was no indication of other endocrinopathies or chronic *Candida* infections, although it is possible other autoimmune diseases may have developed, had she survived.

In the case presented, the low serum cortisol is very supportive of an adrenal crisis. Although 21-hydroxy-

lase antibodies were not tested in this case, the finding of atrophic adrenal glands with dense lymphoplasmacytic infiltration is specific for autoimmune Addison Disease. It is likely that this child initially had sub-clinical AI; no skin hyperpigmentation was seen on exam, and she had been previously healthy (although her underweight status may have been partially due to AI). The clinical history and viral antigen testing suggest that a gastrointestinal rotavirus infection unmasked her disease, causing an adrenal crisis.

## CONCLUSION

This case re-emphasizes that although adrenal insufficiency is a rare diagnosis in childhood, it must be suspected in cases of sudden death, particularly those with a preceding illnesses or surgery.

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