International Journal of Scientific Research Studies

ISSN (print): 3050-6905, ISSN (online): 3050-6913

DOI:10.58806/ijsrs.2026.v3i2n01

Volume 03 Issue 02 February 2026

Page No: 20-30

Primary Adrenal Insufficiency in Autoimmune Rheumatic Diseases: A Systematic Review of Reported Cases and Mechanisms

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ABSTRACT

Background: Primary adrenal insufficiency (PAI) is an uncommon but potentially life-threatening endocrine disorder. Although Addison's disease is classically recognized within autoimmune polyendocrine syndromes, its occurrence in association with autoimmune rheumatic diseases (ARDs) remains poorly characterized and is largely described in case-based literature.

Objective: To systematically synthesize reported cases of confirmed PAI occurring in patients with ARDs and describe clinical patterns, chronology, proposed mechanisms, and outcomes.

Methods: A systematic search of PubMed/MEDLINE, Embase, Web of Science, Scopus, and Google Scholar was conducted from inception to August 2025, without language restrictions. We included case reports, case series, and observational studies with extractable individual-level data reporting confirmed ARD and confirmed PAI. Data were extracted on demographics, ARD type, temporal sequence of diagnoses, clinical presentation, endocrine and imaging findings, immunologic markers (including anti–21-hydroxylase antibodies when available), treatment, and outcomes. Due to heterogeneity and the predominance of descriptive evidence, findings were synthesized narratively.

Results: Thirty-one publications were included, reporting 78 patients with ARD and confirmed PAI. Most cases occurred in women. Systemic lupus erythematosus and antiphospholipid syndrome were the most commonly reported underlying conditions. Two main mechanistic patterns emerged: autoimmune adrenalitis and vascular adrenal injury (hemorrhage/infarction), the latter particularly associated with antiphospholipid syndrome and often presenting with acute adrenal crisis. Across reports, adrenal insufficiency could occur before, after, or concurrently with the rheumatic disease diagnosis, and frequently presented with nonspecific systemic and gastrointestinal symptoms, hypotension, and electrolyte disturbances.

Conclusions: PAI in the context of ARDs is rare but clinically significant and may be under-recognized due to symptom overlap with flares, infections, and treatment-related complications. Early endocrine evaluation and appropriate imaging should be considered in ARD patients presenting with unexplained hypotension, fatigue, gastrointestinal symptoms, or electrolyte abnormalities, particularly when antiphospholipid syndrome is suspected.

ARTICLE DETAILS

Published On:
10 February 2026

KEYWORDS: Primary Adrenal Insufficiency, Addison Disease, Autoimmune Rheumatic Diseases, Autoimmune Adrenalitis, Adrenal Hemorrhage, 21-Hydroxylase Antibodies

Available on:
https://ijsrs.org/

INTRODUCTION

Primary adrenal insufficiency (PAI), traditionally referred to as Addison's disease, is a rare but potentially life-threatening endocrine disorder characterized by inadequate production of glucocorticoids and, in many cases, mineralocorticoids due to dysfunction or destruction of the adrenal cortex [1]. Although the global prevalence remains low, delayed recognition can lead to adrenal crisis, a medical emergency associated with hypotension, shock, electrolyte disturbances, and substantial morbidity and mortality if not

promptly treated [1,2]. In developed countries, autoimmune adrenalitis is the leading cause of PAI, and anti–21-hydroxylase antibodies represent a highly specific biomarker that supports etiologic diagnosis and may precede overt adrenal failure [2,3].

PAI is classically recognized within autoimmune polyendocrine syndromes, particularly autoimmune polyendocrine syndrome type 2 (APS-2), which typically involves Addison's disease in combination with autoimmune thyroid disease and/or type 1 diabetes mellitus [4,5]. This shared autoimmune clustering reflects overlapping genetic susceptibility and immune-mediated pathways. However, despite these well-established endocrine associations, the relationship between PAI and autoimmune rheumatic diseases (ARDs)—including systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), primary Sjögren's syndrome (pSS), systemic sclerosis (SSc), rheumatoid arthritis (RA), and ankylosing spondylitis (AS)—remains incompletely characterized and is still largely confined to scattered case reports and small case series [6,7].

The interface between PAI and ARDs is clinically important for several reasons. First, key manifestations of PAI—fatigue, weight loss, gastrointestinal symptoms, hyperpigmentation, and hypotension—often overlap with systemic autoimmune disease activity, chronic inflammation, anemia, or intercurrent infections, complicating timely recognition in routine practice [1,2]. Second, patients with ARDs are frequently exposed to exogenous glucocorticoids, which makes adrenal dysfunction common in this population; however, glucocorticoid-related suppression primarily leads to *secondary* adrenal insufficiency and must be distinguished from true PAI, particularly in acute settings where misclassification may delay adequate mineralocorticoid replacement or adrenal imaging when vascular injury is suspected [1,2]. Third, ARDs represent a biologically plausible background for adrenal involvement through more than one mechanism, potentially including classic autoimmune adrenalitis as well as vascular and thrombotic injury.

Among ARDs, APS appears to be uniquely associated with acute PAI through vascular adrenal injury, including adrenal venous thrombosis and bilateral adrenal hemorrhage or infarction [8–11]. This pattern differs fundamentally from autoimmune adrenalitis and may lead to abrupt adrenal failure, sometimes serving as the initial manifestation of APS. Conversely, in systemic autoimmune diseases such as SLE and pSS, PAI may occur through autoimmune-mediated adrenal cortex destruction, potentially supported by anti–21-hydroxylase antibody positivity when tested [2,3,12]. Importantly, endocrine autoimmunity may exist along a spectrum: some ARD populations may exhibit adrenal autoantibodies or subtle endocrine abnormalities without overt Addison's disease, raising the hypothesis of "subclinical adrenal autoimmunity" that should be interpreted separately from clinically confirmed PAI cases [12].

Despite the potential clinical relevance of these associations, the available evidence is heterogeneous and dispersed across decades of literature, creating uncertainty regarding clinical patterns, temporal relationships between ARDs and adrenal failure, diagnostic certainty of primary versus secondary adrenal insufficiency, and mechanistic pathways (autoimmune versus vascular) across different rheumatic diseases. A structured synthesis of reported cases may improve clinician awareness, support earlier diagnostic suspicion, and help contextualize adrenal crises in patients with systemic autoimmunity.

Therefore, the objective of this study is to systematically synthesize reported cases of confirmed PAI occurring in association with ARDs, describing clinical presentation, chronology, proposed mechanisms, diagnostic findings, and outcomes. In addition, when applicable, we separately discuss evidence suggesting subclinical adrenal autoimmunity in selected ARDs, while clearly distinguishing such findings from the core dataset of clinically confirmed PAI.

METHODS

Protocol and reporting guideline

This study was conducted as a systematic review of reported cases and case series describing primary adrenal insufficiency (PAI) in the context of autoimmune rheumatic diseases (ARDs). The review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A PRISMA flow diagram summarizing study identification, screening, eligibility assessment, and inclusion is provided.

Eligibility criteria

We defined eligibility criteria a priori.

Types of studies

We included case reports, case series, and observational studies reporting individual-level clinical data on patients diagnosed with both an ARD and confirmed PAI. Systematic reviews were screened only to identify additional primary reports through reference checking, but were not included in the quantitative case pool. Cross-sectional studies evaluating adrenal autoantibodies or adrenal-axis biomarkers without clinically confirmed PAI were not included in the core case dataset and were discussed separately as "subclinical adrenal autoimmunity".

Population

Eligible publications reported patients meeting both of the following:

1. **Autoimmune rheumatic disease (ARD):** systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), primary Sjögren's syndrome (pSS), systemic sclerosis (SSc), rheumatoid arthritis (RA), ankylosing spondylitis/axial spondyloarthritis (AS/axSpA), or overlap syndromes (e.g., SLE+APS).
2. **Primary adrenal insufficiency (PAI):** defined as adrenal cortical failure consistent with Addison's disease or non-autoimmune primary adrenal destruction (e.g., bilateral adrenal hemorrhage/infarction in APS), provided that the diagnosis was supported by endocrine and/or imaging evidence compatible with a primary adrenal process.

Case definition and anti-misclassification framework (primary vs secondary adrenal insufficiency). Because secondary adrenal insufficiency due to exogenous glucocorticoid exposure is common in ARD populations, we applied explicit safeguards to minimize misclassification.

PAI was considered confirmed when at least one of the following diagnostic frameworks was reported:

- **Endocrine confirmation:** low morning serum cortisol with elevated ACTH, and/or an inadequate cortisol response to ACTH stimulation testing, consistent with primary adrenal failure; and/or
- **Mineralocorticoid axis involvement:** clinical/laboratory features supporting primary disease (e.g., hyperkalemia and/or hyponatremia with high ACTH), or documentation of mineralocorticoid deficiency when reported; and/or
- **Imaging/pathologic confirmation:** adrenal computed tomography (CT), magnetic resonance imaging (MRI), or pathology consistent with a primary adrenal process (e.g., bilateral adrenal hemorrhage, infarction, enlargement with hemorrhagic changes, or adrenal atrophy compatible with autoimmune adrenalitis).

We excluded reports where adrenal insufficiency was clearly attributable to: chronic exogenous glucocorticoid use with suspected hypothalamic–pituitary suppression (secondary adrenal insufficiency); pituitary or hypothalamic disease; or infectious or malignant adrenal involvement when explicitly identified as the primary etiology.

Information sources and search strategy

A comprehensive literature search was performed in the following databases from inception to August 2025: PubMed/MEDLINE, Embase, Web of Science, Scopus, and Google Scholar. No language restrictions were applied.

The search strategy combined controlled vocabulary terms (when available) and free-text keywords related to adrenal insufficiency and rheumatic autoimmunity. The core search logic was based on: "Addison disease" OR "primary adrenal insufficiency" OR "adrenal failure") AND ("systemic lupus erythematosus" OR "Sjögren syndrome" OR "systemic sclerosis" OR "rheumatoid arthritis" OR "antiphospholipid syndrome" OR "ankylosing spondylitis" OR "connective tissue diseases").

In addition, the reference lists of included articles and relevant reviews were manually screened to identify further eligible reports not captured in the electronic search.

Study selection

Two reviewers independently screened titles and abstracts retrieved from the search, followed by full-text assessment of potentially eligible reports. Disagreements were resolved through discussion and consensus.

During full-text assessment, studies were excluded primarily for the following reasons: (i) absence of confirmed PAI or insufficient diagnostic support for primary adrenal failure, (ii) absence of confirmed ARD diagnosis or insufficient clinical detail, (iii) adrenal insufficiency attributable to secondary causes (e.g., exogenous glucocorticoids or pituitary disease), (iv) duplicate publications or overlapping cases without additional extractable patient-level information.

Data extraction

From each eligible publication, we extracted individual-level or case-level information when available, including: demographics (age, sex), underlying ARD diagnosis and key rheumatologic features, disease chronology (ARD preceding PAI, PAI preceding ARD, or concurrent onset), clinical manifestations of adrenal insufficiency (e.g., hypotension, hyperpigmentation, gastrointestinal symptoms), endocrine findings (cortisol, ACTH, electrolytes), adrenal imaging findings (CT/MRI when available), adrenal autoantibodies (particularly anti–21-hydroxylase antibodies), proposed pathogenic mechanism (autoimmune adrenalitis vs vascular adrenal injury such as hemorrhage/infarction), and treatment and clinical outcomes (including need for chronic replacement therapy and acute-phase mortality).

Assessment of reporting quality

Given that the evidence base consisted predominantly of case reports and case series, we assessed reporting quality using the CARE guideline framework, with emphasis on diagnostic ascertainment of PAI (primary vs secondary), clarity of ARD diagnosis, completeness of endocrine testing/imaging information, and outcome reporting.

To strengthen interpretability, we also categorized each case by diagnostic certainty for PAI (high, moderate, or low), based on the level of endocrine and imaging evidence provided, and used this framework to support sensitivity interpretation in the discussion.

Data synthesis

Due to heterogeneity in study designs, diagnostic methods, and outcomes—and the predominance of descriptive case-based evidence—quantitative meta-analysis was not feasible. Results were synthesized narratively and organized by underlying ARD category (SLE, APS, pSS, SSc, RA/AS, and overlap presentations). Summary statistics were reported primarily as n/N rather than percentages to minimize misinterpretation in small samples and to acknowledge inherent case-report and publication bias.

RESULTS

A total of 31 articles met the eligibility criteria and were included in this review. Among these, case reports were the most common publication type (n = 25), while small case series (n = 4) and observational studies with extractable individual-level data (n = 2) were also identified. These publications spanned more than seven decades, with the earliest report published in 1950 and the most recent in 2025. The geographic distribution of reports was broad, including North America (n = 12), Europe (n = 10), Asia (n = 6), Africa (n = 2), and South America (n = 1). [21–38]

Across the included literature, a total of 78 patients with autoimmune rheumatic diseases (ARDs) and confirmed primary adrenal insufficiency (PAI) were identified. Female patients accounted for 57/78 cases, and age at PAI diagnosis ranged from 11 to 60 years. The most frequently reported ARDs associated with PAI were systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Sjögren's syndrome, systemic sclerosis (SSc), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). A summary of individual cases and extracted variables is presented in Table 1. [21–38]

Systemic Lupus Erythematosus

A total of 12 patients with SLE were identified across nine reports. In most cases, SLE preceded the diagnosis of Addison's disease/PAI, with a median interval of 2 years between diagnoses. However, in four cases both conditions were diagnosed concurrently, and in two patients Addison's disease represented the initial presentation followed by a later diagnosis of SLE. [21–26]

The most frequently reported manifestations of adrenal insufficiency included fatigue, skin hyperpigmentation, hypotension, and gastrointestinal symptoms such as nausea, vomiting, and abdominal pain. Laboratory abnormalities commonly included hyponatremia and/or hyperkalemia, with endocrine confirmation based on low cortisol and elevated ACTH when available. [21–26]

Mechanistically, two patterns were observed: autoimmune adrenalitis, supported by anti–21-hydroxylase antibody positivity in selected cases, and vascular adrenal involvement in patients with overlapping APS features, in whom adrenal hemorrhage or thrombosis was demonstrated by imaging or autopsy. [21–26]

Antiphospholipid Syndrome

APS was the second most frequently reported ARD associated with PAI, described in 14 patients. In contrast to SLE, most APS cases presented with acute adrenal crisis, frequently accompanied by severe hypotension and shock. In several reports, adrenal insufficiency represented the initial clinical manifestation of APS, preceding other thrombotic events. Radiologic findings commonly included bilateral adrenal enlargement and hyperdense lesions consistent with adrenal hemorrhage, supporting a vascular thrombotic/hemorrhagic mechanism. [8–11,27–31]

Patients typically required immediate stress-dose glucocorticoid replacement and anticoagulation. Outcomes varied across reports and should be interpreted cautiously given the small number of cases and inherent publication bias. [8–11,27–31]

Sjögren's Syndrome

Two distinct patterns were identified in the context of Sjögren's syndrome. First, one cross-sectional study reported anti–21-hydroxylase antibody positivity in a subset of patients with primary Sjögren's syndrome, suggesting possible subclinical adrenal autoimmunity without overt Addison's disease at the time of evaluation. [12]

Second, case reports described patients with Sjögren's syndrome who developed clinically confirmed Addison's disease/PAI, generally occurring years after Sjögren's syndrome onset and supporting a shared autoimmune mechanism in selected patients. [32,33]

Systemic Sclerosis

Three cases of systemic sclerosis associated with PAI were identified, including both adult and pediatric patients. In one case, systemic sclerosis preceded Addison's disease by several years, while in the other two cases the diagnoses were reported concurrently. Presenting features included fatigue, weight loss, and hypotension, with clinical improvement following glucocorticoid replacement therapy in most reports. [33–35]

Rheumatoid Arthritis and Ankylosing Spondylitis

Four historical cases reported the coexistence of Addison's disease/PAI with rheumatoid arthritis (n = 3) and ankylosing spondylitis (n = 1). These cases represent some of the earliest descriptions of adrenal insufficiency in association with inflammatory rheumatic disease, typically occurring after years of rheumatologic manifestations and responding to adrenal hormone replacement. [36–38]

Overlap Presentations

Six patients were identified with overlapping autoimmune rheumatic conditions, including combinations involving SLE, APS, Sjögren's syndrome, systemic sclerosis, and Takayasu arteritis. These complex cases suggest that more than one immunologic or vascular pathway may contribute to adrenal failure in multisystem autoimmunity, and some reports described mixed patterns consistent with both autoimmune adrenalitis and vascular adrenal injury. [33]

DISCUSSION

The coexistence of primary adrenal insufficiency (PAI) and autoimmune rheumatic diseases (ARDs) represents an uncommon but clinically meaningful interface between endocrine failure and systemic autoimmunity. Although Addison's disease is well established within autoimmune polyendocrine syndromes, particularly APS-2, its occurrence alongside ARDs remains largely confined to case reports and small series, limiting inference on true frequency and risk. Nevertheless, the clinical relevance is substantial: adrenal crisis is potentially fatal and its presenting symptoms—fatigue, weight loss, hypotension, gastrointestinal complaints, and electrolyte disturbances—frequently overlap with manifestations of ARDs, infection, or drug-related complications, which can delay recognition and appropriate replacement therapy. Contemporary endocrine guidance emphasizes that diagnostic confirmation of PAI should rely on endocrine testing (low cortisol with elevated ACTH and/or inadequate response to stimulation) and—where appropriate—imaging to identify destructive or hemorrhagic adrenal processes. [1–3]

A key contribution of this synthesis is the delineation of two mechanistically distinct pathways through which PAI may arise in ARD populations. The first mirrors classic autoimmune adrenalitis, in which immune-mediated adrenal cortical destruction evolves over time and may be supported by anti–21-hydroxylase antibodies when assessed. This pathway is biologically plausible given the shared genetic susceptibility and clustering of organ-specific autoimmunity across autoimmune conditions, as discussed in foundational work on autoimmune adrenal insufficiency and polyendocrine syndromes. [3–5] The second pathway is vascular adrenal injury—hemorrhage and/or infarction—most prominently observed in antiphospholipid syndrome (APS), where thrombosis-related adrenal venous congestion and hemorrhagic necrosis can result in abrupt adrenal failure. [8–11] Importantly, these mechanisms may overlap, particularly in systemic autoimmunity where APS features coexist with SLE or other ARDs, and the same patient may display both immune-mediated and thrombotic/vascular contributions to adrenal damage. [21–33]

Within the case-based literature, SLE emerged as the most frequently reported ARD associated with PAI. In these reports, adrenal insufficiency often occurred after the diagnosis of SLE, but synchronous presentation and cases in which adrenal failure preceded SLE were also documented. [21–26] Clinically, this association is challenging because SLE itself can present with constitutional symptoms and hemodynamic instability, and acute adrenal crisis may be misattributed to lupus flare, infection, gastrointestinal involvement, or medication effects. [2,6,21–26] In addition, a major confounder in rheumatology practice is that glucocorticoids are widely used, making secondary adrenal insufficiency common and creating risk of misclassification if primary versus secondary etiologies are not carefully distinguished. [1,2] For this reason, the diagnostic features that support true PAI—particularly elevated ACTH, electrolyte patterns compatible with mineralocorticoid deficiency, and imaging evidence of adrenal atrophy or destructive processes—should be explicitly documented whenever possible. [1–3] In pragmatic terms, the intersection of SLE and suspected adrenal insufficiency should prompt a low threshold for paired morning cortisol and ACTH testing and electrolyte evaluation, complemented by imaging when hemorrhage/infarction is suspected, especially in patients with antiphospholipid antibodies or thrombotic manifestations. [1,2,15,21–26]

APS represents a distinctive and clinically urgent subgroup in which PAI is frequently linked to vascular adrenal injury. Several reports describe acute adrenal crisis as the sentinel manifestation of APS, sometimes preceding classic thrombotic events such as deep vein thrombosis or pulmonary embolism. [8–11,27–31] Imaging patterns described across APS cases—including bilateral adrenal enlargement and hyperdense lesions—are consistent with hemorrhage/infarction, supporting a thrombotic/hemorrhagic mechanism rather than classic autoimmune adrenalitis. [10,11,27–31] Management in this setting requires immediate stress-dose glucocorticoids (and mineralocorticoid replacement when indicated) together with a careful anticoagulation strategy once clinically stable, recognizing the competing risks of thrombosis and bleeding. [1,2,8–11] Importantly, outcomes should be communicated using counts rather than percentages given the small number of published cases and likely publication bias; in the available APS case dataset summarized here, fatal outcomes were reported in 4/14 cases, typically during the acute phase. This should be interpreted cautiously as a marker of severity in reported cases rather than a population-level fatality estimate. [27–31]

The Sjögren's disease findings underscore the importance of separating clinically confirmed PAI from the broader "adrenal autoimmunity spectrum." A cross-sectional study reported anti–21-hydroxylase antibody positivity in a subset of primary Sjögren's

syndrome patients without overt PAI at evaluation, suggesting subclinical adrenal autoimmunity. [12] This observation is clinically intriguing and may reflect shared autoimmune clustering; however, it does not constitute Addison's disease/PAI and should not be pooled numerically with confirmed PAI cases. The natural history of progression from adrenal autoantibody positivity to overt adrenal failure in Sjögren's syndrome remains uncertain, and longitudinal studies would be needed to define predictive value, absolute risk, and optimal monitoring strategies. [3,12] At the same time, the presence of published cases of overt Addison's disease in patients with Sjögren's syndrome suggests that true PAI can occur in selected individuals, particularly in the context of broader autoimmune overlap. [32,33]

Although systemic sclerosis (SSc), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) were less frequently represented, their inclusion broadens the clinical spectrum of ARD contexts in which PAI may occur. The SSc cases highlight that fatigue, hypotension, and weight loss—often attributed to systemic disease burden—may also reflect adrenal failure and can improve substantially with appropriate hormone replacement once recognized. [33–35] Historical reports of PAI in RA and AS emphasize that such associations have been observed for decades, but also illustrate the modern diagnostic challenge: RA patients are frequently treated with glucocorticoids, which heightens the need to differentiate secondary adrenal suppression from true primary gland failure, ideally with ACTH-based interpretation and supportive imaging where relevant. [1,2,36–38]

Overlap presentations—such as combinations involving SLE, APS, Sjögren's syndrome, systemic sclerosis, and vasculitides—suggest that multiple immune-mediated and vascular mechanisms may converge within a single patient. [33] From a pathophysiologic standpoint, this supports a framework in which clinicians should consider (i) autoimmune adrenalitis, (ii) vascular adrenal injury (especially in APS), and (iii) mixed phenotypes. In practice, pairing endocrine testing with imaging, and integrating antibody profiles (including antiphospholipid antibodies and anti–21-hydroxylase when available), can help distinguish likely mechanisms and tailor management priorities. [1–3,8–12,15]

This review has several strengths. First, it assembles case-based evidence spanning more than seven decades into an organized disease-specific synthesis, enabling pattern recognition across heterogeneous reports. Second, it highlights mechanistic divergence—autoimmune adrenalitis versus thrombotic/hemorrhagic adrenal injury—providing clinically actionable framing, particularly relevant to APS. [3,8–11] Third, by summarizing chronology, clinical presentation, imaging, and immunologic testing in a standardized dataset (Table 1), it provides a practical reference for clinicians encountering suspected adrenal insufficiency in ARD patients. [21–38]

Limitations are primarily driven by the nature of the evidence. Most data derive from case reports and small series with variable diagnostic detail, inconsistent endocrine testing (including incomplete ACTH reporting or lack of stimulation testing), and heterogeneous imaging documentation. Publication bias is likely, favoring severe and unusual presentations, and limiting any attempt to infer incidence or relative risk. To address these issues and align with best practice for case-based evidence, structured reporting quality assessment using CARE principles is appropriate; however, future syntheses would be strengthened by explicitly presenting a diagnostic certainty framework (e.g., high/moderate/low certainty of primary adrenal failure based on endocrine and imaging evidence) and summarizing the distribution of certainty levels in supplementary material. [20] Additionally, ARD definitions in older reports may predate modern classification criteria; mapping historical descriptions to contemporary criteria can improve interpretability but cannot eliminate classification uncertainty. [14–19]

CONCLUSION

In conclusion, primary adrenal insufficiency in autoimmune rheumatic diseases is uncommon but clinically consequential, particularly when presenting as adrenal crisis. The available evidence suggests two main mechanistic patterns: autoimmune adrenalitis and vascular adrenal injury, the latter being especially relevant in antiphospholipid syndrome. Because adrenal failure may mimic rheumatic disease flares or infections—and because secondary adrenal insufficiency related to glucocorticoid exposure is frequent in this patient population—clinicians should maintain diagnostic vigilance and prioritize timely endocrine evaluation, electrolyte assessment, and adrenal imaging when appropriate. Future multicenter registries and prospective studies are warranted to improve diagnostic standardization, clarify the adrenal autoimmunity spectrum in systemic rheumatic disease, and better define outcomes across disease subgroups.

Table 1. Reported cases of primary adrenal insufficiency associated with autoimmune rheumatic diseases, stratified by underlying diagnosis, clinical presentation, pathogenic mechanism, and outcomes.

Author, year	Study design	Country	N	Age, sex	Rheumatic disease	Disease duration	Order of appearance (time)	Addison/PAI manifestations (summary)	Anti-adrenal antibodies	Cortisol level	Diagnostic certainty (PAI)	Outcome
Bhat et al., 2014	Case report	India	1	20, female	SLE	ND	Simultaneously	Anorexia; hyperpigmentation (face/hands); fever; vomiting; BP 90/60; abdominal CT normal	Positive (3 U/mL; NR <1)	7.5 µg/dL (NR >15)	Moderate	Good
Saba et al., 1969	Case report	Italy	1	53, female	SSc	6 years	SSc → AD	Hyperpigmentation; asthenia; adynamia; Na 130; K 5.2; hypotension	ND	ND	Low	Death (cardiac and gastrointestinal complications)
Eichner et al., 1973	Case report	USA	1	26, female	SLE	ND	AD → SLE (4 years)	Back pain; vomiting; fever; hyperpigmentation; BP 50/30; HR 130; Na 119; K 3.6; eosinophils 15%	Positive	ND	Moderate	Bad
Ellman & Cudkowicz, 1952	Case report	UK	1	53, female	RA	5 years	RA → AD	Fatigue; vomiting; anorexia; weight loss; hyperpigmentation (face/neck); fasting glucose 61 mg/dL	ND	ND	Low	Good
Caughey & McCoy, 1951	Case report	New Zealand	1	58, male	RA	15 years	RA → AD (16 years)	Salt craving; nausea/vomiting; thin hair; diffuse hyperpigmentation; eosinophils 11%	ND	ND	Low	Good
Godswill & Odigie, 2014	Case report	Nigeria	1	29, female	SLE	5 months	Simultaneously	Postural dizziness; weakness; vomiting; weight loss; fever; dehydration; hyperpigmentation (palms/oral/knuckles); HR 114; BP 85/60 (postural drop); Na 121; K 5.8; CT: bilateral adrenal atrophy	Positive (1:100; NR <1:10)	95 nmol/L (NR 140–550)	High	Good

Author, year	Study design	Country	N	Age, sex	Rheumatic disease	Disease duration	Order of appearance (time)	Addison/PAI manifestations (summary)	Anti-adrenal antibodies	Cortisol level	Diagnostic certainty (PAI)	Outcome
Kosková et al., 2005	Case report	Slovakia	1	11, female	SSc	3 years	Simultaneously	Vomiting; abdominal pain; fatigue; BP 95/60; tachycardia; adrenal MRI normal	Negative	20 nmol/L	Moderate	Good
Satta et al., 2000	Case report	UK	1	60, male	APS	ND	AD → APS (3 months)	Weakness; fatigue; anorexia; hypotension; anemia; eosinophilia; hyponatremia; hyperkalemia; adrenal CT normal	Negative	110 nmol/L (NR 200–700)	Moderate	Good
Mavragani et al., 2012	Cross-sectional	Greece	63	58.1±11.6, 94% female	pSS	8.6±7.0 years	Not overt PAI	No patient had adrenal insufficiency; anti–21-hydroxylase positive in 17.5%	Positive in 17.5%	ND	Not applicable	Not applicable
Zellissen et al., 1995	Cohort (AD cohort)	Netherlands	2/83	Mean 45.3, 66% female	Sjögren's syndrome	8 years	AD → SS (2.5 years)	ND	82.7% in cohort	ND	Low	ND
Zhang et al., 2009	Retrospective study	China	6	35.2 (28–49), 50% female	Overlap (SLE/TA/APS+AS/SLE+pSS/SSc)	79.4 (12–180) months	2 simultaneous; 3 AID→AD (9 years); 1 AD→AID (4 years)	Fatigue (2/6); hyperpigmentation (5/6); appetite loss (2/6); depression (2/6); weight loss (2/6); CT/MRI: 3 normal, 1 hemorrhage, 1 unilateral nodule, 1 bilateral enlargement with hypodense lesion	ND	Median 31.5 (8.9–126) mcg/L (NR 50–200)	Moderate	Good
Robinson CEG, 1957	Case report	Canada	1	50, male	AS	ND	AS → AD (2 years)	Fatigue; hyperpigmentation; weight loss; BP 90/40	ND	ND	Low	Good
Koren & Hanly, 1997	Case report	Canada	1	39, female	SLE	ND	SLE → AD (2 years)	ND	ND	ND	Low	ND
Kuster &	Case report	Switzerland	1	44, NR	SLE	ND	SLE → AD (2 years)	Weight loss; weakness;	ND	ND	Low	ND

Author, year	Study design	Country	N	Age, sex	Rheumatic disease	Disease duration	Order of appearance (time)	Addison/PAI manifestations (summary)	Anti-adrenal antibodies	Cortisol level	Diagnostic certainty (PAI)	Outcome
Merlo, 1999								diarrhea; fever; hyponatremia				
Asherson & Hughes, 1989	Case report	UK	1	43, male	Primary APS	10 years	APS → AD	Hyperpigmentation (skin/buccal)	ND	ND	Low	ND
Carette & Jobin, 1989	Case report	Canada	1	34, male	Primary APS	17 years	APS → AD	Fever; hyperpigmentation; abdominal tenderness; hypotension; Na 117; K 6.1	ND	49.7 nmol/L (NR 190–700)	High	Good
Perera & Ragan, 1950	Case report	USA	1	55, male	RA	10 years	RA → AD	Weakness; hyperpigmentation (skin/buccal); disappearance of hypertension	ND	ND	Low	Good
Takebayashi et al., 2003	Case report	Japan	1	48, female	Primary APS	33 years	APS → AD	Severe hypotension; fever; fatigue; hypoglycemia; Na 121	Negative	<1.0	High	Good

aβ2GPI, anti–β2-glycoprotein I antibody; aCL, anticardiolipin antibody; ACTH, adrenocorticotropic hormone; AD, Addison's disease; ANA, antinuclear antibody; APS, antiphospholipid syndrome; AS, ankylosing spondylitis; AS/axSpA, ankylosing spondylitis/axial spondyloarthritis; BP, blood pressure; CT, computed tomography; DVT, deep vein thrombosis; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; HR, heart rate; IgG, immunoglobulin G; IgM, immunoglobulin M; K, potassium; MRI, magnetic resonance imaging; MS, multiple sclerosis; Na, sodium; ND, not described; NR, not reported; PAI, primary adrenal insufficiency; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TA, Takayasu arteritis.

DECLARATIONS

Author Contribution: Jozélio Freire de Carvalho and Rodrigo Antonio Brandao Neto has contributed to the conception and design of the study, literature search, data extraction and interpretation, and drafting and critical revision of the manuscript. Both authors approved the final version and agree to be accountable for all aspects of the work.

Funding: No funding or sponsorship was received for this study or for the publication of this article.

Artificial intelligence (AI) use: AI-assisted software (ChatGPT, OpenAI) was used exclusively for language editing and to improve clarity. No content generation, data extraction, or reference creation was performed using AI tools. The authors take full responsibility for the manuscript.

Data Availability: All data generated or analyzed during this study are derived from previously published articles that are cited in the reference list and are available in the public domain.

Ethics approval and consent to participate: Not applicable. This study is based exclusively on previously published literature and does not involve human participants, animals or identifiable data.

Conflict of Interest: Jozélio Freire de Carvalho has nothing to disclose. Rodrigo Antonio Brandao Neto has nothing to disclose.

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