Review Article

# Immune Reconstitution Inflammatory Syndrome Following Remission of Cushing's Syndrome and Review of Literature

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## Abstract

The current study aims to report cases of immune reconstitution inflammatory syndrome (IRIS) following Cushing's syndrome (CS) treatment and elucidate various presentations of IRIS and its management. A single-centre study was conducted in individuals with endogenous CS who presented with immune reconstitution inflammatory syndrome after CS remission. A literature review was also conducted to describe the previous reporting of IRIS. Nine cases from the author's centre were identified. Out of 9 cases, one case was ectopic CS, who presented with CNS vasculitis following excision of the primary lesion. Other 8 cases were Cushing's disease (CD) presented with diverse IRIS manifestations in the form of thyroiditis, oculomotor neuritis, extraocular muscle palsy, episcleritis, bell's palsy, rheumatoid arthritis (RA) and Charcot neuroarthropathy, with the time of presentation from less than 1 month till 24 months. The most common IRIS described in the literature is thyroid dysfunction, and the time of presentation of IRIS is variable from less than one month to 5 years. Immune reconstitution inflammatory syndrome is a unique and rare post-operative complication after CS remission, affecting various organ systems due to rebound immunity.

**Keywords:** Autoimmune dysfunction, Cushing's syndrome, immune reconstitution inflammatory syndrome

## Introduction

Patients with Cushing's syndrome (CS) suffer from alterations in the function of the immune system both during the active phase and remission.[1] Chronic hypercortisolism in CS induces immune suppression, often leading to serious complications such as opportunistic infections and sepsis. This immune suppression results in rebound phenomena when CS is treated, manifesting as excessive immune response and sometimes autoimmunity known as immune reconstitution inflammatory syndrome (IRIS).[2] Various autoimmune conditions have been described, which could be new onset or exacerbation of previous autoimmune conditions, including autoimmune thyroid disease, rheumatoid arthritis (RA), celiac disease, sarcoidosis, systemic lupus erythematosus, vitiligo, atopic dermatitis, and psoriasis.[1]

## Materials and Methods

Nine cases of CS who had IRIS were taken for study. The diagnosis of CS was based on clinical features, cortisol excess, failure to decrease plasma cortisol after dexamethasone suppression test (DST), radiographic imaging, and histological confirmation of the tumour. We extracted baseline demographics and clinical characteristics, including age at admission, sex, weight, body mass index, symptom duration before the presentation, and the clinical manifestations of the disease. Cortisol dynamics, including 8 am (171–536 nmol/L) and 11 pm plasma cortisol (<207 nmol/L) with 8 am ACTH (6–60 pg/mL), DST including 1 mg overnight [ONDST (<50 nmol/L)] and two-days 2-mg low-dose DST [LDDST (<50 nmol/L)] and two-days 8-mg high-dose DST [HDDST (>50% suppression of the baseline 8 am cortisol)], were performed as per laid down on standard procedure.[3] Neuroimaging of the pituitary gland was performed using dedicated Sellar magnetic resonance imaging protocols (CEMRI 3 Tesla;

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Siemens Magnetom). Post-operative 8 am cortisol (from day 1 to day 7), histopathology of the tumour tissue, anterior pituitary hormones post-operatively, and cortisol at 3 months (8 am and 11 pm cortisol) were assessed. A literature search was done from 1990 to date by using the keywords 'Cushing's syndrome', 'remission', 'IRIS', and 'autoimmune dysfunction' by searching PubMed/MEDLINE. The language was restricted to English. The references of relevant case reports and case series were also screened for potential articles. Only case reports and case series were included. In this descriptive study, categorical variables are expressed as percentages. Normally distributed continuous variables are expressed as mean ± standard deviation (SD).

## Results

All nine cases were ACTH-dependent CS, including one ectopic ACTH-secreting tumour. The mean age of the patients was 33.6 ± 11.9 years, and the female: male ratio was 7:2. The average time of development of IRIS was 10.6 months, ranging from 1 month up to 24 months. The autoimmune diseases (IRIS) were one patient with thyroiditis, four patients with RA (of these four patients, two also had Charcot arthropathy and lateral rectus palsy),one patient with CNS vasculitis, one patient with episcleritis, one patient with oculomotor neuritis, and one patient with Bell's palsy. The clinical and demographic profiles of the nine studied patients are shown in Table 1.

### Case 1

A 35-year-old male presented with an increasing dark complexion for the last 6 months [Figure 1], easy fatiguability, and altered behaviour for 20 days. He was disoriented to time and place and had generalised hyperpigmentation and significant proximal muscle weakness. An ill-defined lump of around 6 cm × 6 cm was felt at the left hypochondriac region. He had hypokalaemia, hypoalbuminemia, elevated transaminases, hypocalcaemia, and metabolic alkalosis. His morning cortisol was 2509 nmol/L with an ACTH of 1398 pg/mL, with non-suppressible ONDST and LDDST. Because of the short duration of symptoms, severe proximal myopathy, hyperpigmentation, hypokalaemia, metabolic alkalosis, and ACTH >90 pg/mL, ectopic ACTH-dependent CS was kept as the first possibility. Contrast-enhanced computed tomography of the abdomen showed a 7.9 cm × 7 cm heteroechoic mass in the tail of the pancreas [Figure 2]. A 10 cm × 5 cm well-encapsulated mass adherent to duodenojejunal flexure, free from the pancreas, smooth surface with feeder vessels from the splenic artery, was visualised during surgery. Post-operatively, his cortisol, ACTH and serum potassium normalised. Histopathology revealed a paraganglioma.

Ten days after surgery, he experienced slurring, facial asymmetry, and altered sensorium, followed by gait imbalance, visual blurring, and weakness of limbs. Investigations, including cerebrospinal fluid analysis, ACTH, and serum cortisol levels, were normal. Pan uveitis with retinal vasculitis of the left eye was noted. Contrast-enhanced MRI brain revealed multiple bilateral infarcts [Figure 3]. CT angiography was suggestive of vasculitis. Immunological and infective workups were negative. The patient was managed with three pulses of injection methylprednisolone, followed by cyclophosphamide (15 mg/kg) and oral prednisolone (1 mg/kg). On follow-up, the patient had remarkable improvement in visual acuity with reduced ocular inflammation, improved speech, and was able to walk with support.

### Case 2

A 19-year-old male presented with a 4-year history of weight gain, facial plethora, abdominal striae, and easy bruisability.

**Table 1: Clinical characteristics of 9 patients with IRIS after CS remission**

| Parameter | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 35 | 19 | 34 | 35 | 56 | 42 | 40 | 22 | 20 |
| Sex | Male | Male | Female | Female | Female | Female | Female | Female | Female |
| Number of discriminatory features of CS | 1 | 4 | 4 | 4 | 2 | 2 | 3 | 2 | 3 |
| 8 am cortisol (nmol/L) | 2509 | 1185 | 1414 | 1200 | 611 | 619 | 1200 | 760 | 1100 |
| 11 pm cortisol (nmol/L) | - | 964 | - | 1200 | 577 | 292 | 442 | 700 | 760 |
| ONDST (nmol/L) | 1750 | 964 | 957 | 1200 | 615 | 144 | 300 | - | 720 |
| LDDST (nmol/L) | - | 1282 | 623 | 1200 | 249 | 146 | 170 | 560 | 960 |
| HDDST (nmol/L) | - | 710 | 256 | 700 | 62 | 16 | - | 360 | 130 |
| ACTH pg/ml | 1398 | 24 | 44 | 36 | 61 | 24 | 139 | 34 | 24 |
| CEMRI sella (micro-adenoma/Macro-adenoma | Ectopic source | Micro-adenoma | Macro-adenoma | Micro-adenoma | Micro-adenoma | Micro-adenoma | Macro-adenoma | Micro-adenoma | Micro-adenoma |
| Immediate post-op cortisol | 361 | 41 | 611 | 136 | 73 | 17 | 109 | 85 | 41 |
| Type of IRIS | CNS vasculitis | Thyroiditis | Oculomotor neuritis | Lateral rectus palsy, RA | Charcot arthropathy, RA | Episcleritis | RA | Bells palsy | RA |
| Duration of onset of IRIS following surgery (months) | 1 | 4 | 24 | 12 | 1 | 12 | 18 | 12 | 12 |

CS: Cushing's syndrome; ONDST: Overnight dexamethasone suppression test; LDDST: Low-dose dexamethasone suppression test; HDDST: High-dose dexamethasone suppression test; ACTH: Adrenocorticotropic hormone; IRIS: Immune reconstitution inflammatory syndrome; RA: Rheumatoid arthritis

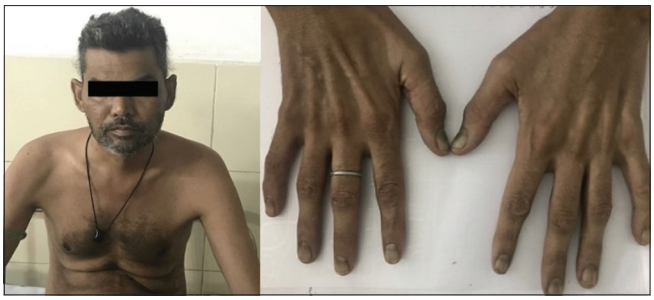

**Figure 1:** Generalised hyperpigmentation and hyperpigmentation of hands

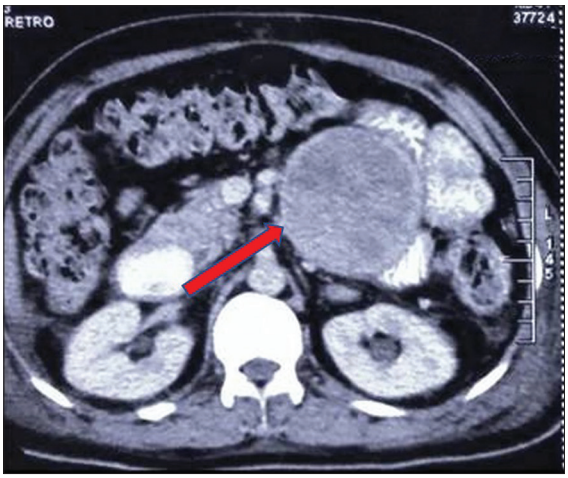


**Figure 2:** CECT abdomen showing mass in the tail of the pancreas (red arrow)

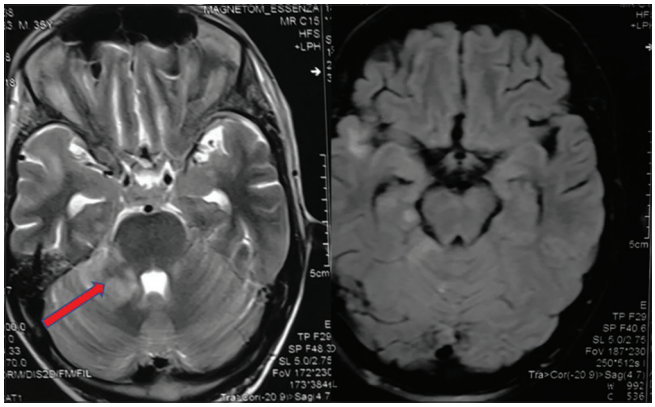

**Figure 3:** Multiple hyperintense lesions in bilateral cerebral and cerebellar hemispheres (red arrow), some showing diffusion restriction as well as post-contrast enhancement

He had cuticular atrophy and proximal muscle weakness, and pre-operatively also found to have diabetes and hypertension. On hormonal evaluation, his 8 am cortisol was 1185 nmol/L with ACTH of 24 pg/mL, 11 pm cortisol 964 nmol/L, and non-suppressible ONDST and LDDST. CEMRI sella was suggestive of microadenoma. He underwent transsphenoidal surgery (TSS), and the post-operative period was uneventful. His immediate post-operative cortisol was 41 nmol/L, suggestive of remission and was thus started on hydrocortisone replacement. However, 4 months post-surgery, he presented with inappropriate weight loss, palpitations, and loss of appetite. His pulse rate was 94/min, tremors were present, and he had non-tender grade 1 goitre. Further workup revealed T3- 2.2 ng/mL, T4- 18.1 mcg/dL, TSH- 0.001 mIU/mL, TPO- 15 IU/L, and $^{99m}$Tc thyroid scan: Uptake- 0.1%. In view of the above, a diagnosis of sub-acute thyroiditis was made, and he was started on propranolol. Thyroid function at 12 weeks was suggestive of hypothyroidism; thus, he was started on levothyroxine (LT4).

## Case 3

A 39-year-old female presented with a 3-year history of hirsutism, weight gain, blurring of vision, and irregular menstrual cycles. On examination, she had features of florid CS. On hormonal evaluation, her morning cortisol was 1414 nmol/L with an ACTH of 44 pg/mL. 11 pm cortisol was 740 nmol/L, along with non-suppressible ONDST and LDDST. CEMRI sella revealed pituitary macroadenoma (16 mm ×13 mm ×16.5 mm). The patient underwent TSS. There was no remission post-operatively (post-operative cortisol >600 nmol/L). Because of biochemical non-remission, she was started on ketoconazole, which was stopped after 3 months due to raised liver enzymes. She underwent gamma knife surgery the same year. In the meantime, she was started on other medical management. With that, her cortisol normalised as measured by urinary free cortisol and she developed drooping of the right eyelid, double vision, and mild coryza accompanied by high-grade fever. There was no pain or lacrimation. On examination, she had right 3$^{rd}$-nerve palsy, unilateral ptosis, and dilated non-reactive pupil. CE MRI-brain revealed linear enhancement of the right oculomotor nerve, suggestive of neuritis. CSF examination showed normal cell counts with raised protein (97 mg/dL). She received intravenous immunoglobulin (2 gm/kg) over 5 days. Her symptoms gradually improved and she became asymptomatic in the next 3 weeks.

## Case 4

A 35-year-old lady presented with a 3-year history of progressive weight gain and oligomenorrhoea. She had a history of progressive proximal myopathy, increased facial hair growth, severe acne, and easy bruisability of 6 months duration. She was also detected to be hypertensive and diabetic during her hospital stay. Hormonal evaluation revealed both 8 am and 11 pm cortisol >1200 nmol/L with ACTH of 36 pg/mL. ONDST and LDDST were non-suppressible, and HDDST was 700 nmol/L. CEMRI of the sella was suggestive of microadenoma on the left side of the pituitary and CT abdomen suggestive of bilateral adrenal hyperplasia. She underwent TSS. Post-operative cortisol at day 3 was 136 nmol/L. There was improvement in hyperpigmentation, proximal myopathy, striae, and ecchymosis, with resolution of hypertension and diabetes. However, 1 year after surgery, there was a rise in 11 pm cortisol with non-suppressible ONDST. Repeat MRI sella revealed a 2-mm residual lesion on the lateral aspect of the pituitary. Because of this, ketoconazole was started and she underwent gamma knife surgery. One

year after gamma knife surgery, she experienced joint pain with morning stiffness, but RF and anti-CCP serology were negative. She was diagnosed with a case of seronegative RA and started on methotrexate and hydroxychloroquine, with significant symptomatic improvement. At present, she is in remission with 8 AM cortisol of 277 nmol/L and 11 pm cortisol of 77 nmol/L.

### Case 5

A 56-year-old lady presented with a 2-year history of thinning of limbs, abdominal obesity, and proximal myopathy. She was a known case of endogenous depression and hypertension for 8 years, deforming RA (on methotrexate) for 5 years, and type 2 DM for 5 years. Her 8 AM cortisol was 609 nmol/L, and 11 pm cortisol was 577 nmol/L with an ACTH of 61 pg/mL. ONDST (615 nmol/L) and LDDST (249 nmol/L) were non-suppressible with HDDST of 62 nmol/L (>50% suppression). The positive IV anti-diuretic hormone (ADH) stimulation test was suggestive of pituitary-dependent CS. Subsequently, CEMRI sella was suggestive of microadenoma on the left half of the pituitary. Because of the very subtle clinical features of CS and the background of endogenous depression, the possibility of pseudo-CS was kept. However, the insulin tolerance test and loperamide challenge test ruled out that possibility. Hence, a diagnosis of Cushing's disease (CD) was made. She underwent TSS. On post-operative day 1, her 8 am cortisol was 73.9 nmol/l, and she was started on hydrocortisone replacement. One month post-surgery, she had an RA flare-up in the form of increasing pain, swelling, and stiffness of small joints. She also developed pain and swelling over her left foot. There was a temperature difference between the left and right foot. Inflammatory markers were raised in the form of high ESR and CRP. MRI of the left foot revealed marrow oedema and bony erosions involving tarsals and metatarsals, with disruption of multiple joints, tendinosis, and subluxation of the first MTP joint, suggestive of acute Charcot neuroarthropathy (CN). In view of the disease flare of RA, she was started on prednisolone and hydroxychloroquine. For Charcot arthropathy, she was placed on a non-removable total contact cast (TCC) along with an injection of zoledronic acid. After 3 months of TCC, her foot temperature normalised, small joint arthritis resolved, and she was prescribed hydrocortisone replacement and modified footwear. At present, she is in remission for CD.

### Case 6

A 42-year-old female presented with a 3-year history of significant weight gain, increased facial hair, and proximal muscle weakness. Her 8 am cortisol was 619 nmol/L, 11 pm cortisol 292 nmol/L, ONDST 144 nmol/L, LDDST 146 nmol/L, and HDDST >50% suppressed (16 nmol/L), with ACTH of 24 pg/mL. CEMRI was suggestive of microadenoma on the left half of the pituitary. She underwent TSS. Immediate post-operative cortisol was 17 nmol/L, and she was placed on hydrocortisone replacement therapy. One year post-surgery, she presented to the eye department with pain and redness in both eyes. She was diagnosed as a case of episcleritis and treated with topical NSAIDs. Her symptoms resolved in 1 week. At present, the patient continues to be in remission on hydrocortisone supplementation.

### Case 7

A 40-year-old female presented with a 1-year history of classic features of CS. Hormonal evaluation revealed 8 am cortisol 1200 nmol/L, 11 pm cortisol 442 nmol/L, ONDST 300 nmol/L, LDDST 170 nmol/L, and ACTH 139 pg/mL. MRI of the sella was suggestive of macroadenoma on the right half of the pituitary. Immediate post-operative cortisol post TSS was 109 nmol/L, and she was started on hydrocortisone replacement. After a year and a half of surgery, she developed joint pains with stiffness. She was diagnosed with seronegative RA, started on disease-modifying anti-rheumatic drugs (DMARDs), and found relief.

### Case 8

A 22-year-old female presented with classical features of CS of 3 years duration. Hormonal workup showed 8 am cortisol 760 nmol/L, 11 pm 700 nmol/L, LDDST 560 nmol/L, HDDST 360 nmol/L, and ACTH of 34 pg/mL. CEMRI sella was suggestive of microadenoma on the right side of the pituitary. She underwent TSS and went into remission. One year post-surgery, she developed weakness in the right half of the face, which was lower motor neuron type suggestive of Bell's palsy. Her symptoms resolved with a short course of prednisolone and physiotherapy. At present, she is in remission for CS.

### Case 9

A 20-year-old female presented features of CS of 8 years duration. At presentation, she was severely hypercortisolic with 8 am cortisol 1100 nmol/L, 11 pm cortisol 964 nmol/L, ONDST 964 nmol/L, LDDST 1282 nmol/L, and ACTH 24 pg/mL. CEMRI of the sella was suggestive of microadenoma in the right half of the pituitary. She underwent TSS, immediate post-op cortisol was 41 nmol/L, and she was started on hydrocortisone replacement. One year post-surgery, she started developing generalised aches and pains with small- and large-joint arthritis with associated significant early morning stiffness. She was diagnosed as a case of seronegative RA and started on DMARDs with symptomatic relief.

## Discussion

In our case series, we presented nine patients with new onset or exacerbation of previous autoimmune conditions after remission. We found that the mean time of development of IRIS was 10.6 months, with the majority of patients being female. We are also reporting one case of CNS vasculitis and one case of CN, which has never been described before.

IRIS post-CS remission is sparingly described in the literature and can be either unmasking or paradoxical IRIS.[4] Previous case reports/series have described new-onset psoriasis,[5] sarcoidosis,[6] systemic lupus erythematosus,[7] Grave's disease,[5] primary biliary cirrhosis,[8] and retinal vasculitis,[9] on

remission of CS. Of all the IRIS manifestations, autoimmune thyroid disease is probably the most common.[10] Indeed, researchers had previously reported thyroid dysfunction after treatment of CS.[11] Herein, we have summarised the various IRIS after disease remission to date [Table 2].

Chronic hypercortisolism causes an immunosuppressive state, leading to severe complications such as opportunistic infections and sepsis by interfering with the host defence system and affecting the innate immune system, including cellular and humoral components.[2] The subclass of T-helper (Th) cells, Th1 and Th2, are components of adaptive immunity. Th1 cells are the primary agents of cellular immunity, whereas Th2 cells are modulators of humoral immunity. Glucocorticoids suppress Th1 responses, causing an increase in susceptibility to intracellular and opportunistic infections, and promote Th2 responses, which could explain the possible development of certain autoimmune diseases. Thus, it is an imbalance of Th1/Th2 cells, which could lead to a rebound autoimmune response during remission of CS.[12] This feature of activation of the immune system, which has been suppressed previously, leads to the development of an autoimmune disease known as IRIS.

Abnormal thyroid function, including Graves' disease (GD) and autoimmune thyroiditis, are well documented as IRIS after initiation of anti-retroviral therapy (ART).[13] Similarly, it has also been documented after treatment of CS.[14] The pathogenic mechanisms are speculative, but there may be rapid restoration of cellular immunity leading to the recruitment of memory CD4 T cells, causing autoimmune thyroid disease.[15] In addition, restored immunity against antigens from infecting micro-organisms causes thyroid tissue damage.

New or worsening rheumatologic symptoms can follow remission of CS.[5,6,8,16] Joint pain is a common symptom in rheumatological disorders, with RA being the most commonly documented.[17] High endogenous cortisol can suppress RA symptoms and rheumatoid factor production.[18] Thus, the diagnosis is mainly clinical based on symmetrical progressive inflammatory arthropathy with or without positive serology. Early diagnosis and intervention provide the greatest hope of reducing the associated disability. In the context of rheumatologic and immunologic disorders, CNS involvement with vasculitis in the setting of HIV infection as IRIS has been described before.[19] However, CNS vasculitis in the CD remission setting is not yet known. CNS vasculitis can be seen in various disorders, including malignancies.[20,21] In the index case, the possibilities of metastasis from primary paraganglioma, paraneoplastic syndrome, infections, or a demyelinating pathology were considered initially. Brain MRI with an angiogram with or without vascular imaging can identify CNS vasculitis. However, common radiological mimickers need exclusion.[22,23] CNS vasculitis requires aggressive treatment with glucocorticoids and steroid-sparing induction agents such as cyclophosphamide. Azathioprine, methotrexate, or mycophenolate mofetil are used in maintenance phase. Radiological imaging can be repeated every 3–6 months for resolution.[22,23]

**Table 2: Review of literature and cases of IRIS after treatment of CS**

| Author (ref) | Publication | Autoimmune disorder (IRIS) | Number of patients |
|---|---|---|---|
| N Takasu (1990)[14] | Case series | Transient hyperthyroidism, hypothyroidism | 3 |
| R Candrina (1992)[30] | Case report | CD | 1 |
| N Takasu (1993)[31] | Case series | Transient hyperthyroidism, Transient hypothyroidism | 2 |
| JL Senecal (1994)[32] | Case report | RA | 1 |
| F Yakushiji (1995)[18] | Case report | RA | 1 |
| A Steuer (1995)[33] | Case report | Sarcoidosis | 1 |
| Takenaka K (1995)[34] | Case report | Sarcoidosis | 1 |
| Marzano AV (1998)[35] | Case report | Sarcoidosis | 1 |
| Y Noguchi (1998)[36] | Case report | SLE | 1 |
| SI Muzulu (1998)[37] | Case report | Polymyalgia rheumatica | 1 |
| Maldonado M (1999)[38] | Case report | Sarcoidosis | 1 |
| A Colao (2000)[10] | Case series | Autoimmune thyroid dysfunction | 20 |
| Mussig K (2004)[39] | Case report | GD | 1 |
| Fichtel JC (2006)[40] | Case report | Sarcoidosis | 1 |
| R Awazawa (2007)[24] | Case report | Pemphigus vulgaris | 1 |
| F da Mota (2011)[8] | Case series | Psoriasis, Sarcoidosis, PBC, GD, Asthma, Eczema, Skin rash, Rosacea | 11 |
| D Bongetta (2016)[6] | Case report | Sarcoidosis | 1 |
| JEF Diernaes (2016)[16] | Case report | Sarcoidosis | 1 |
| L Petramala (2018)[5] | Case series | GD, Hashimoto thyroiditis, SLE, Myasthenia gravis, Temporal arteritis, Psoriasis, RA | 9 |
| Tatsi C (2018)[41] | Case series | CD, Asthma, Psoriasis, Vitiligo, Hashimoto thyroiditis, Optic neuritis, Neuropathy, GD | 10 |
| R Richstein (2022)[42] | Case report | RA | 1 |

IRIS: Immune reconstitution inflammatory syndrome; CD: Celiac disease; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; GD: Graves disease; PBC: Primary biliary cirrhosis

Autoimmune disorders affecting the skin, such as vitiligo, eczema, psoriasis, and pemphigus vulgaris, have also been described.[8,24] These disorders may present as a new-onset rash or a change in the morphology of the previously identified rash, leading to a change in diagnosis.[24]

CN is a morbid condition that places patients at risk for poor outcomes and sometimes leads to amputation if not properly managed. Its etiopathogenesis is intriguing. Initially, neurotraumatic and neurovascular theories were proposed. Still, recently, the understanding of CN has changed based on the evidence that there is activation of RANK by RANKL, which incites multiple inflammatory cytokines locally, the most common being tumour necrosis factor-α (TNF-α), interleukin-1ß (IL-1β), and interleukin-6. This leads to locally raised cytokines.[25] Activation of the suppressed immune system after treatment of CS may have a similar effect on increasing local cytokines in an already predisposed diabetic foot.[26] Whatever the cause, treatment is mainly mechanical offloading, good glycaemic control if the patient is diabetic, and sometimes adjunctive therapy such as bisphosphonates or denosumab.

Ocular IRIS with various manifestations such as optic neuritis, papilledema, uveitis, orbital myositis, keratitis, non-specific orbital inflammation, and retinitis have been described in the setting of HIV/AIDS and non-HIV conditions.[27,28] Paralysis of the oculomotor nerve is a rare presentation of IRIS.[29] In the case of multiple oculomotor nerve damage in young subjects, two other differential diagnoses should also be considered: multiple sclerosis and Tolosa-Hunt's syndrome. Treatment of ocular IRIS depends on the underlying aetiology, which involves supportive care and anti-microbials. In some cases, prednisolone 1–2 mg/kg or equivalent may be prescribed for a few weeks.

## Conclusion

CS is associated with many co-morbidities and increased risk of mortality, but with effective treatment, most patients normalise cortisol secretion, with improvement in the clinical picture, including co-morbidities and mortality risk. However, there are chances that these patients may develop IRIS after resolution of hypercortisolism. IRIS may have varied presentations, and we must be aware of this entity to initiate prompt diagnosis and treatment.

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### Author contribution

M.M.B. collected the data, did the data analysis, reviewed the literature and created the tables and figures. U.A., T.P., K.B.D. and L.D. helped edit and write the manuscript. R.W. conceived the idea of the study, managed the patients, and edited the final manuscript. S.K.B. supervised patient management and helped in the final editing of the manuscript. A.S. provided rheumatological expertise and helped in the management of patients.

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### Conflicts of interest

There are no conflicts of interest.

## References

1. Hasenmajer V, Sbardella E, Sciarra F, Minnetti M, Isidori AM, Venneri MA. The immune system in Cushing's syndrome. Trends Endocrinol Metab 2020;31:655–69.
2. Cheng VCC, Yuen KY, Chan WM, Ma ESK, Chan RMT. Immunorestitution disease involving the innate and adaptive response. Clin Infect Dis 2000;30:882–92.
3. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, *et al*. The diagnosis of cushing's syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008;93:1526–40.
4. Makhoul J, Uppal S, Siegel M. Double trouble: Concomitant unmasking and paradoxical immune reconstitution inflammatory syndrome in a patient with newly diagnosed HIV. IDCases 2022;28:e01482.
5. Petramala L, Olmati F, Conforti MG, Concistré A, Bisogni V, Alfieri N, *et al*. Autoimmune diseases in patients with Cushing's syndrome after resolution of hypercortisolism: Case reports and literature review. Int J Endocrinol 2018;2018:1–7.
6. Bongetta D, Zoia C, Lombardi F, Lovati E, Lucotti P, Gaetani P. Systemic sarcoidosis unmasked by Cushing's disease surgical treatment. Case Rep Med 2016;2016:1–3.
7. Schneider J, Zatarain E. IRIS and SLE. Clin Immunol 2006;118:152–3.
8. Da Mota F, Murray C, Ezzat S. Overt immune dysfunction after Cushing's syndrome remission: A consecutive case series and review of the literature. J Clin Endocrinol Metab 2011;96:E1670–4.
9. Rehman HU, Walton C, Atkin S. Cushing's disease masking coincidental steroid-responsive diseases. Postgrad Med J 1999;75:43–5.
10. Colao A, Pivonello R, Faggiano A, Filippella M, Ferone D, Di Somma C, *et al*. Increased prevalence of thyroid autoimmunity in patients successfully treated for Cushing's disease. Clin Endocrinol (Oxf) 2000;53:13–9.
11. Jiang S, Yang C, Feng M, Yao Y, Deng K, Xing B, *et al*. Management of thyrotoxicosis occurring after surgery for Cushing's disease: A case series. Gland Surg 2021;10:1627–37.
12. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: State of the art. Lancet Diabetes Endocrinol 2016;4:611–29.
13. Ayad S, Gergis K, Mirza N, Rayad MN, Salamera J. Graves' Disease in a Patient With Human Immunodeficiency Virus Infection as an Immune Reconstitution Inflammatory Syndrome. Cureus 2021. Available from: https://www.cureus.com/articles/59477-graves-disease-in-a-patient-with-human-immunodeficiency-virus-infection-as-an-immune-reconstitution-inflammatory-syndrome. [Last accessed on 2024 Jan 22].
14. Takasu N, Komiya I, Nagasawa Y, Asawa T, Yamada T. Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome due to an adrenocortical adenoma. N Engl J Med 1990;322:1708–12.
15. Visser R, De Mast Q, Netea-Maier RT, Van Der Ven AJAM. Hashimoto's thyroiditis presenting as acute painful thyroiditis and as a manifestation of an immune reconstitution inflammatory syndrome in a human immunodeficiency virus–seropositive patient. Thyroid 2012;22:853–5.
16. Diernaes JEF, Bygum A, Poulsen PL. Unmasking sarcoidosis following surgery for Cushing disease. Dermatoendocrinol 2016;8:e983688.
17. Cai Y, Zhang J, Liang J, Xiao M, Zhang G, Jing Z, *et al*. The burden of rheumatoid arthritis: Findings from the 2019 global burden of diseases study and forecasts for 2030 by Bayesian age-period-cohort analysis. J Clin Med 2023;12:1291.
18. Yakushiji F, Kita M, Hiroi N, Ueshiba H, Monma I, Miyachi Y. Exacerbation of rheumatoid arthritis after removal of adrenal adenoma in Cushing's syndrome. Endocr J 1995;42:219–23.
19. Rushing EJ, Liappis A, Smirniotopoulos JD, Smith AB, Henry JM, Man YG, *et al*. Immune reconstitution inflammatory syndrome of the

brain: Case illustrations of a challenging entity. J Neuropathol Exp Neurol 2008;67:819–27.
20. Allegri P, Rissotto R, Herbort CP, Murialdo U. CNS diseases and uveitis. J Ophthalmic Vis Res 2011;6:284–308.
21. Brown RD, Christianson TJH, Huston J, Ansell SM, Giannini C, Hunder GG. Primary central nervous system vasculitis associated with lymphoma. Neurology 2018;90:e847-55.
22. Salvarani C, Brown RD, Calamia KT, Christianson TJH, Weigand SD, Miller DV, *et al*. Primary central nervous system vasculitis: Analysis of 101 patients. Ann Neurol 2007;62:442–51.
23. Salvarani C, Brown RD, Hunder GG. Adult primary central nervous system vasculitis. Lancet 2012;380:767–77.
24. Awazawa R, Yamamoto Y, Gushi M, Taira K, Yagi N, Asato Y, *et al*. Case of pemphigus foliaceus that shifted into pemphigus vulgaris after adrenal tumor resection. J Dermatol 2007;34:549–55.
25. Das L, Rastogi A, Prakash M, Dutta P, Bhansali A. Differential abatement of inflammation and osteoclastogenesis in active charcot neuroarthropathy: Mechanistic insights from randomized controlled study. In Review; 2021. Available from: https://www.researchsquare.com/article/rs-181871/v1. [Last accessed on 2024 Jan 22].
26. Rizzo P, Pitocco D, Zaccardi F, Di Stasio E, Strollo R, Rizzi A, *et al*. Autoantibodies to post-translationally modified type I and II collagen in Charcot neuroarthropathy in subjects with type 2 diabetes mellitus. Diabetes Metab Res Rev 2017;33:e2839.
27. Chiabo J, Nahon-Esteve S, Alketbi M, Lassalle S, Tieulie N, Martel A. Orbital non-HIV immune reconstitution inflammatory syndrome after cytapheresis. Eur J Ophthalmol 2021;31:NP85–8.
28. Otiti-Sengeri J, Meenken C, Van Den Horn GJ, Kempen JH. Ocular immune reconstitution inflammatory syndromes: Curr Opin HIV AIDS 2008;3:432–7.
29. Atipo-Tsiba P, Kombo BE. Immune reconstitution inflammatory syndrome and shingles associated with a combined paralysis of three oculomotor nerves: A case report. Ethiop J Health Sci 2016;26:297.
30. Candrina R, Di Stefano O. Exacerbation of celiac disease after cure of cushing's disease. Am J Med 1993;95:341.
31. Takasu N, Ohara N, Yamada T, Komiya I. Development of autoimmune thyroid dysfunction after bilateral adrenalectomy in a patient with Carney's complex and after removal of ACTH-producing pituitary adenoma in a patient with Cushing's disease. J Endocrinol Invest 1993;16:697-702.
32. Senécal J, Uthman I, Beauregard H. Cushing's disease-induced remission of severe rheumatoid arthritis. Arthritis Rheum 1994;37:1826-6.
33. Steuer A, Cavan DA, Lowy C. Sarcoidosis presenting after resection of an adrenocortical adenoma. BMJ 1995;310:567-8.
34. Takenaka K, Yanase T, Takayanagi R, Haji M, Ikuyama S, Nawata H. Cushing's disease preceding sarcoidosis. Intern Med 1995;34:580-3.
35. Goihman-Yahr M. Correspondence. Int J Dermatol 1998;37:798-8.
36. Noguchi Y, Tamai H, Fujisawa K, Nagano J, Mukuta T, Komaki G, et al. Systemic lupus erythematosus after pituitary adenomectomy in a patient with Cushing's disease. Clin Endocrinol (Oxf) 1998;48:670-2.
37. Muzulu SI, Howlett TA. Polymyalgia rheumatica presenting after successful treatment of Cushing's disease. Rheumatology 1998;37:804-5.
38. Maldonado M, Orlander P, Roshan SY, McCutcheon IE, Cleary KR, Friend KE. Sarcoidosis after surgically induced remission of Cushing's disease. Endocr Pract 1999;5:43-5.
39. Müssig K, Gallwitz B, Häring H, Seif FJ. Manifestation of thyroid autoimmunity in patients successfully treated for hypercortisolism. Clin Endocrinol (Oxf) 2004;61:284-4.
40. Fichtel JC, Wiggins Duckworth AK, Soares T, Lesher JL. Subcutaneous sarcoidosis presenting after treatment of Cushing's disease. J Am Acad Dermatol 2006;54:360-1.
41. Tatsi C, Keil M, Lyssikatos C, Belyavskaya E, Stratakis C, Lodish M. Incidence of autoimmune and related disorders after resolution of endogenous cushing syndrome in children. Horm Metab Res 2018;50:290-5.
42. Richstein R, Schulman-Rosenbaum R. PSUN42 new-onset rheumatoid arthritis after surgical treatment of cushing syndrome. J Endocr Soc 2022;6 (Suppl_1):A129-30.