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Original Article

Suspected drug-induced hypersensitivity reaction (DRESS Syndrome) following sitagliptin addition in a diabetic patient on glimepiride and metformin: A case report.

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Abstract

Background

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare, potentially life-threatening drug-induced hypersensitivity reaction characterized by skin eruptions, eosinophilia, and multi-organ involvement. While rare with antidiabetic drugs, sitagliptin has been implicated in a few reported cases.
Objective : To report and analyze a suspected case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome associated with sitagliptin initiation in a type 2 diabetic patient previously controlled on glimepiride and metformin, and to emphasize the importance of early recognition, appropriate management, and pharmacovigilance in rare but serious drug-induced hypersensitivity reactions**.**

Case Presentation

We present a case of suspected DRESS syndrome in a 52-year-old male with type 2 diabetes mellitus, who developed facial and limb swelling, skin hyperpigmentation, and systemic laboratory abnormalities five days after sitagliptin initiation.

Management and Outcome

Sitagliptin was discontinued, and supportive care was initiated. Laboratory abnormalities included leukocytosis, eosinophilia (10%, AEC 1,480 /µL), elevated liver enzymes, and mild renal dysfunction. Symptoms resolved within two weeks following drug withdrawal.

Conclusion

This case highlights the need for vigilance in recognizing drug-induced hypersensitivity reactions in diabetic patients, even with relatively safe agents like sitagliptin.

Recommendation

Sitagliptin should be used cautiously after assessing hypersensitivity risk. Monitor for early DRESS signs (rash, facial swelling, eosinophilia) within 2–4 weeks. Educate patients, perform baseline and follow-up labs. Stop the drug at first suspicion; avoid rechallenge and other DPP-4 inhibitors. Report to pharmacovigilance. Skin biopsy and viral tests may aid diagnosis. Further research is needed.

Keywords: *Drug Reaction with Eosinophilia and Systemic Symptoms syndrome, Sitagliptin, Glimepiride, Metformin, Adverse drug reaction, Hypersensitivity*
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Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (**DRESS syndrome**) is a severe hypersensitivity reaction that can result in significant morbidity and mortality, with an estimated mortality rate of up to 10% [1]. It typically presents with a delayed onset of 2–8 weeks after drug exposure and includes skin eruptions, haematological abnormalities (notably eosinophilia), and systemic organ involvement such as hepatitis and nephritis [2]. Although antidiabetic medications are rarely implicated, a few cases of sitagliptin-induced DRESS have been reported [3]. Early recognition and prompt discontinuation of the causative drug are crucial to prevent complications.

Objective

To report and analyze a suspected case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome associated with sitagliptin initiation in a type 2 diabetic patient previously controlled on glimepiride and metformin, and to emphasize the importance of early recognition, appropriate management, and pharmacovigilance in rare but serious drug-induced hypersensitivity reactions.

Case presentation

A 52-year-old male with a history of type 2 diabetes mellitus was previously controlled on glimepiride and metformin. Due to poor glycemic control (random blood sugar 526 mg/dL), sitagliptin was added to his regimen.
Ten days after initiating sitagliptin, the patient developed progressive facial swelling, bilateral upper and lower limb edema, and pruritic skin hyperpigmentation and thickening on the forearm. He did not report fever or lymphadenopathy.

On examination

General: Facial puffiness, bilateral limb edema.
Skin: Diffuse hyperpigmentation and scaling on the forearm, no ulceration or blistering.
Systemic examination: No lymphadenopathy or hepatosplenomegaly.

Figure no. 1: Suspected sitagliptin induces DRESS syndrome

Diffuse hyperpigmentation and scaling on the forearm, no ulceration or blistering

Laboratory investigations

CBC: Hemoglobin 13.2 g/dL, TLC 14,800 /µL (leukocytosis), eosinophils 10%, AEC 1,480 /µL.
Liver function tests: Total bilirubin 1.2 mg/dL, AST 92 U/L, ALT 112 U/L, ALP 185 U/L.

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Renal function tests: Creatinine 1.5 mg/dL, BUN 32 mg/dL.

Random blood sugar: 364 mg/dL (urine sugar positive).

Based on the temporal relationship of symptom onset with sitagliptin initiation, characteristic eosinophilia, elevated liver enzymes, and mild renal impairment, a diagnosis of probable DRESS syndrome was made (WHO-UMC causality assessment).

Management and Outcome

Sitagliptin was immediately discontinued. Supportive care with oral cetirizine 10 mg once daily and topical mometasone furoate 0.1% cream applied twice daily was initiated. No side effects were observed with these medications. Blood glucose was controlled with continued metformin and glimepiride, monitored closely for further adverse effects. The patient's symptoms, including facial and limb edema and skin changes, resolved within two weeks of sitagliptin withdrawal. Laboratory parameters also gradually normalized.

Table 1: Case summary

Parameter	Findings
Patient Age/Sex	52-year-old male
Location	Berhampur, Odisha ,India
Past Medical History	Type 2 diabetes mellitus, previously on glimepiride and metformin
Initial Blood Sugar	Random Blood Sugar: 526 mg/dL (before therapy change)
New Therapy Added	Sitagliptin was added to the existing regimen of glimepiride and metformin.
Onset of Symptoms	10 days after sitagliptin initiation
Presenting Complaints	Facial puffiness, swelling of upper/lower limbs, and forearm skin thickening
Skin Findings	Diffuse hyperpigmentation, scaling, thickening (no blistering/ulceration)
Systemic Examination	No fever, lymphadenopathy, or hepatosplenomegaly
CBC	TLC: 14,800 /µL (↑), eosinophils: 10% (↑), AEC: 1,480 /µL (↑)
LFTs	AST: 92 U/L (↑), ALT: 112 U/L (↑), ALP: 185 U/L (mild ↑), bilirubin: 1.2 mg/dL (mild ↑)
RFTs	Creatinine: 1.5 mg/dL (mild ↑), BUN: 32 mg/dL (mild ↑)
Blood Glucose at Presentation	RBS: 364 mg/dL
Provisional Diagnosis	Suspected DRESS syndrome induced by sitagliptin
WHO-UMC Causality	Probable
Management	Immediate discontinuation of sitagliptin, supportive care, and glucose monitoring
Outcome	Resolution of symptoms within 2 weeks post-drug withdrawal

Table No:-2: Detailed causality assessment (WHO-UMC Criteria)

Criteria	Assessment & Findings
1. Temporal Relationship	The patient developed symptoms (facial swelling, limb edema, skin thickening) 10 days after adding sitagliptin to pre-existing therapy (glimepiride and metformin). This timing is consistent with the early phase of DRESS reactions.
2. Dechallenge	Sitagliptin was immediately discontinued upon suspicion of drug reaction. The patient's symptoms improved significantly, and lab markers (eosinophilia, LFTs, renal function) started to normalize within 2 weeks of withdrawal.
3. Rechallenge	Not performed, as it is unethical and contraindicated to reintroduce the suspected offending drug in DRESS syndrome due to potential life-threatening reactions.
4. Alternative Causes	- No history of new infections, recent travel, or alternative exposures. - No known history of autoimmune disease. - No history of other new medications, herbal supplements, or environmental allergens.
5. Previous Knowledge of ADR	Sitagliptin has been rarely reported to cause severe cutaneous adverse reactions (SCARs), including DRESS syndrome [3,5]. Glimepiride and metformin have not been linked to DRESS.

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6. Laboratory/Objective Evidence	- CBC: Leukocytosis (TLC 14,800 /µL), eosinophilia (10%, AEC 1,480 /µL) - LFTs: Elevated AST, ALT, mild bilirubin and ALP elevation - RFTs: Mildly elevated creatinine and BUN - Skin exam: characteristic changes
7. Previous Reaction Reports	DRESS syndrome with sitagliptin has been documented in literature (though rare), strengthening the likelihood of a causal relationship in this scenario [3,5].
8. Consistency with Pharmacology	The patient's reaction pattern aligns with the delayed-type hypersensitivity reaction known to occur with DPP-4 inhibitors, involving immune activation and possible viral reactivation [4].

Discussion

DRESS syndrome is a delayed-type hypersensitivity reaction associated with various drugs, including anticonvulsants, antibiotics, and rarely, antidiabetic agents [1,2]. Sitagliptin, a DPP-4 inhibitor, has been reported in a few cases to cause severe cutaneous adverse reactions (SCARs), including DRESS [3]. The pathogenesis involves drug-specific T-cell activation and reactivation of herpesviruses (e.g., HHV-6) [4]. The RegiSCAR diagnostic criteria (not fully assessed here due to lack of biopsy or viral testing) typically comprise fever, lymphadenopathy, eosinophilia, organ involvement, plus skin eruption [5].
This case was characterised as probable DRESS based on:

- Recent initiation of sitagliptin
- Facial edema, skin pigmentation changes
- Marked eosinophilia (AEC 1,480 /µL)
- Liver dysfunction (AST, ALT elevations)
- Renal dysfunction (mild creatinine elevation)

Early secession of the suspected drug and supportive management typically leads to resolution, but systemic corticosteroids may be necessary in severe cases [6].

Generalizability

This case report adds to the limited but growing body of evidence linking sitagliptin, a widely used DPP-4 inhibitor, to rare but serious hypersensitivity reactions such as DRESS syndrome. It underscores the importance of post-marketing surveillance and pharmacovigilance in identifying adverse drug reactions even in commonly prescribed medications. Although the findings cannot be broadly generalized due to the single-patient nature of the report, they provide valuable clinical insights for practitioners managing diabetic patients on sitagliptin, especially in resource-limited settings.

Conclusion

Clinicians should maintain a **high index of suspicion** for DRESS syndrome in patients who develop systemic symptoms and skin reactions after starting new medications, including sitagliptin. Early recognition and discontinuation of the causative drug are crucial to prevent life-threatening complications.

Limitations of the study

The study is limited by its single-case nature, which restricts generalizability and prevents causal inference. Histopathological confirmation and viral reactivation tests were not performed, reducing diagnostic certainty based on RegiSCAR criteria. Genetic predisposition assessments, such as HLA typing, were not conducted. Potential environmental or infectious risk factors were not fully evaluated. Follow-up was limited to short-term recovery, and long-term outcomes remain unknown. Additionally, immunological tests like lymphocyte transformation or patch testing were unavailable to confirm drug-specific hypersensitivity.

Recommendations

1. Avoid empirical use of sitagliptin in uncontrolled hyperglycemia without risk-benefit assessment

Sitagliptin should be added cautiously in poorly controlled diabetic patients, especially in combination with other oral hypoglycemic agents, and only after evaluating for potential hypersensitivity risks.

2. Monitor for hypersensitivity signs within the first 2 Weeks

Clinicians should monitor for early signs of DRESS syndrome, such as unexplained facial edema, skin changes, and eosinophilia during the first 2–4 weeks of therapy with sitagliptin or any new antidiabetic drug.

3. Educate Patients and Caregivers on Warning Signs

Patients initiating sitagliptin should be informed about potential adverse effects and advised to seek immediate medical attention if they experience swelling, rash, itching, fever, or fatigue.

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4. Routine baseline and follow-up lab testing

Baseline CBC with differential, liver, and renal function tests should be considered before initiating sitagliptin. Follow-up labs within 7–10 days may help identify early changes suggestive of hypersensitivity.

5. Discontinue the Suspected Drug at First Suspicion of DRESS

At the first clinical or laboratory suspicion of DRESS, immediate discontinuation of sitagliptin is recommended. Delayed withdrawal may worsen organ involvement and increase morbidity.

6. Avoid Rechallenge With Suspected Drug

Rechallenge with sitagliptin or similar agents is strongly discouraged once DRESS syndrome is suspected or confirmed, due to the risk of recurrence or worsening of symptoms.

7. Consider DPP-4 Inhibitor Cross-Reactivity

In patients with sitagliptin-induced DRESS, alternative DPP-4 inhibitors (e.g., linagliptin, saxagliptin) should be used with caution or avoided altogether due to possible class-effect hypersensitivity.

8. Report the Adverse Drug Reaction to Pharmacovigilance Authorities

This case should be reported to the Pharmacovigilance Programme of India (PvPI) or other relevant regulatory authorities to enhance post-marketing surveillance and drug safety monitoring.

9. Consider Biopsy or Viral Testing for Diagnostic Confirmation (if feasible)

In future suspected DRESS cases, performing skin biopsy and viral reactivation panels (e.g., HHV-6) may support the diagnosis and contribute to the differential diagnosis of other SCARs.

10. Encourage Further Research on Sitagliptin-Induced SCARs

Given the rarity of reported cases, larger pharmacovigilance analyses or multicenter case series are encouraged to assess the true incidence and risk factors for sitagliptin-induced DRESS.

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Conflict of Interest

The authors declared no conflict of interest.

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List of abbreviations

DRESS Drug Reaction with Eosinophilia and Systemic Symptoms
ADR: Adverse Drug Reaction
SCARs: Severe Cutaneous Adverse Reactions
WHO-UMC World Health Organization – Uppsala Monitoring Centre
CBC Complete Blood Count
TLC Total Leukocyte Count
AEC Absolute Eosinophil Count
LFT Liver Function Test
AST Aspartate Aminotransferase
ALT Alanine Aminotransferase
ALP Alkaline Phosphatase
RFT Renal Function Test
BUN Blood Urea Nitrogen
RBS Random Blood Sugar
HHV-6 Human Herpesvirus 6
PvPI Pharmacovigilance Programme of India
DPP-4 Dipeptidyl Peptidase-4
RegiSCAR Registry of Severe Cutaneous Adverse Reactions

Authors' Contribution

Dr. Suvendu Kumar Panda: Conceptualization, case identification, literature review, manuscript drafting, and final editing. Served as the corresponding author and coordinated communication among co-authors and institutional departments.

Dr. Snehasini Dash: Data collection, patient follow-up, contribution to the case summary and causality assessment tables, and manuscript writing (case presentation and outcome sections).

Dr. Srikanta Panigrahy: Conducted critical literature review on DRESS syndrome, assisted in data interpretation, and contributed to the discussion and recommendation sections.

Dr Manisha Panda: Data collection, patient follow-up, contribution to the case summary and causality assessment tables, and manuscript writing (case presentation and outcome sections).

Dr. Jasmine Mahanta: Provided clinical insights into diagnostic approach and differential diagnosis, assisted in editing the introduction and methodology.

Dr. Mousumi Pradhan: Helped in data verification, formatting of tables and references, and review of pharmacovigilance-related content.

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