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Case Report

Multisystemic Adverse Reactions to Amlodipine Mimicking Vasculitis

Sudipto Chakraborty [1,*], Debroop Sengupta [2], Mohidur Rahaman [1], Pradip Dey [1], Saibal Moitra [1], Dhiman Sen [1]

[1] Apollo Multispecialty Hospitals, Kolkata, West Bengal, India.
[2] Institute of Post Graduate Medical Education & Research (IPGME&R) and Seth Sukhlal Karnani Memorial (SSKM) Hospitals, Kolkata, West Bengal, India.

* Correspondence: sudipto.ipgmer@gmail.com.

Abstract: A 52-year-old lady, with hypothyroidism and hypertension for the last 2 months, presented with complaints of low-grade fever, gum hypertrophy, abdominal pain, palpable purpura, bilateral knee joint swelling, and bruising of both lower legs for the last 1 month. She had a significant fall in haemoglobin, a high Reticulocyte count, increased bilirubin level, and persistently high potassium with a positive Direct Coombs test. After the initial assessment, she was clinically diagnosed with an Adult-onset Henoch-Schonlein Purpura. She underwent skin biopsy, suggestive of Drug Rash- Amlodipine being implicated as the drug causing multisystemic manifestations. She was treated conservatively. Amlodipine was discontinued, and oral ketone and bilastine were started. She had a complete recovery.

Keywords: Amlodipine; Henoch Scholein Purpura; Drug Rash.

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1. Introduction

Amlodipine is a long-acting Dihydro-pyridine Calcium Channel blocker and is used to treat hypertension, and helps to prevent future heart attacks, heart diseases, and stroke. The usual dose is 5mg and 10mg and can be taken once or twice daily. Side effects of amlodipine are extensive; common side effects include headache, dizziness, flushing, palpitation, swollen ankles, etc. Serious side effects include pancreatitis, hepatitis, and liver disease. Life-threatening side effects include anaphylaxis. The above list is not exclusive and excludes other side effects [1].

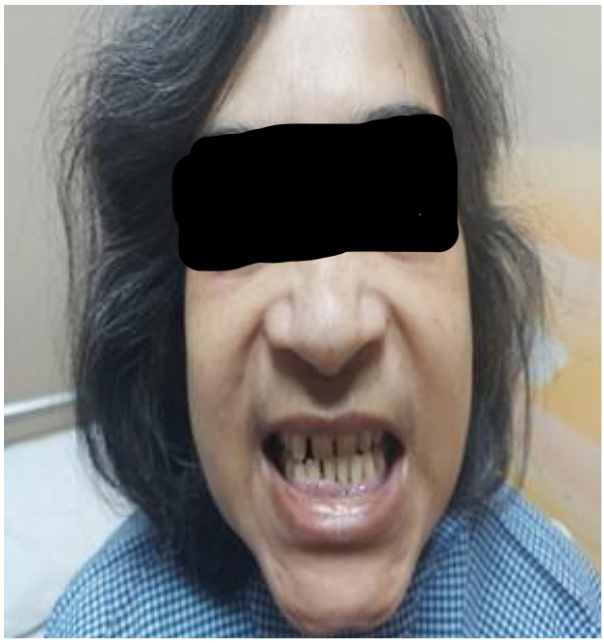
Henoch-Schonlein Purpura (HSP) is an immune complex-mediated small vessel vasculitis with predominant IgA deposits. Clinical manifestations include purpura, arthralgia or arthritis, enteritis, and glomerulonephritis. HSP is more common in children, but the disease is more severe in adults since the initial severity of disease presentation does not correlate with the outcome [2].

2. Case Report

A 52-year lady with hypothyroidism and hypertension on regular Amlodipine 5mg and Thyroxine sodium 75mcg, both initiated 2 months back, presented with a history of low-grade fever, gum hypertrophy, pain in the abdomen, bilateral knee joint swelling, palpable purpuric spots and bruising in both lower legs for the last 1 month. She complained that her fever was 100°F for 1 month, insidious in onset, continuous in nature, and reduced after taking paracetamol. Gum hypertrophy (Figure 1) was also present for the same duration, which was insidious in onset and gradually progressive. Abdominal pain

was episodic, with exacerbations upon fasting. Purpuric spots were present mainly in the lower extremities, and they were palpable. Bruising was present mainly in the periorbital region and the lower extremities. She also complained of painful, swollen, erythematous, tender areas in both lower limbs, including the knee joint.

Figure 1. Showing gum hypertrophy on Day 6 of admission.



She did not complain about any history of anorexia, weakness, significant weight loss, pruritus, night sweats, bone pain, yellowish discolouration of eyes and urine, neck or armpit swelling, altered sensorium, respiratory distress, chest pain, palpitation, malar rash, reduced urination, hematuria or any joint pain. She did not have a history of Tuberculosis or Tuberculosis contact or a similar history in the family. She had attained menopause 6 years ago. On Examination, she was conscious, alert, and cooperative. Positive examination findings included pallor and icterus present. Upon skin examination, there were palpable purpuric spots present mainly in the lower limbs (Figure 2), and they were non-blanchable. She had bruising spots mainly in the periorbital region and lower limbs. Bilateral knee joint swelling is present. Pulse rate: 110/min; Respiratory rate: 21/min; BP 106/62 mmHg; SpO_2 94% in room air and temperature 99.6°F (Table 1). Systemic examination: no abnormality detected.

Table 1. Report chart during hospital stay.

Exams	Day of Admission					
	Day 1	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 10**
Haemoglobin (13-15 Gm/Dl)	7.7	7	6.2	7.1	7.4	7.6
Reticulocyte Count (0.5-1%)	-	7% (Corrected)	-	-	-	-
Direct Coombs' Test (-)	-	Positive	-	-	-	-
TLC (4000-11000/Cu Mm)	3700	3000	2500	3600	3000	3200
Platelet (1.5-4 lac/Cu Mm)	2.31	1.93	1.76	1.64	1.76	2.51
INR (1-1.4)	-	1.2	-	-	-	-
Sodium (135-145 Meq/L)	131	135	133	135	136	133

Potassium (3.5-5.5 Meq/L)	5.2	6.1	5.8	5.5	4.6	4.8
Albumin (3.8-4.6 Gm/Dl)	3.2	2.5	2.8	2.8	3	3.1
Globulin (2-3.5 Gm/Dl)	3.2	2.6	2.7	3.2	3.3	3.7
Total Bilirubin (0.2-1.2 Mg/Dl)	3.5	4.1	3.4	3	2	1.6
Unconjugated Bilirubin (0.2-0.8 Mg/Dl)	2.8	3.4	2.8	2.3	1.7	1.2
SGOT/SGPT/ALP (U/Dl)	14	11	-	-	18	36
SGPT (0-40 U/Dl)	8	6	-	-	6	9
ALP (40-180 IU/Dl)	52	44	-	-	46	68
TSH (0.5-5 MIU/L)	-	17	-	-	-	-
Serum 8 AM Cortisol (5-25 Mcg/Dl)	-	12.8	-	-	-	-
LDH (100-250 U/L)	-	3107	-	-	-	-
Urine Routine Examination (-)	-	WNL	-	-	-	-
Urine Albumin-Creatinine Ratio (<30)	-	10	-	-	-	-
Stool Occult Blood Test (-)	-	WNL	-	-	-	-
Blood Culture (-)	-	No Growth	-	-	-	-
Urine Culture (-)	-	No Growth	-	-	-	-
Serum IgA (0.8-4 Gm/L)	-	3.1	-	-	-	-
Serum IgE (150-300 IU/mL)	-	47.5	-	-	-	-
HBsAg (-)	-	NR	-	-	-	-
Anti-HCV (-)	-	NR	-	-	-	-
HIV 1 & 2 (-)	-	NR	-	-	-	-
Malaria Parasite Dual Antigen (-)	-	NR	-	-	-	-
Scrub Typhus IgM (-)	-	NR	-	-	-	-
Leptospira IgM (-)	-	NR	-	-	-	-
ANA (-)	-	NR	-	-	-	-
C-ANCA (PR3) and P-ANCA (MPO) (-)	-	NR	-	-	-	-
C3 (75-175 Mg/Dl)	-	88	-	-	-	-
C4 (16-48 Mg/Dl)	-	27	-	-	-	-
Ferritin (20-250 Ng/mL)	-	125	-	-	-	-
Anti-dsDNA (-)	-	NR	-	-	-	-

Legend.: WNL. within normal limit. NR. non-reactive.

She was admitted, all investigations were sent, and treatment was initiated conservatively, including IV Fluids and Amlodipine, which was discontinued immediately after admission. A Chest X-ray was done, which was normal. USG of the abdomen detected grade I fatty liver. A punch biopsy was taken from the purpuric spot on the legs after a dermatological consultation on Day 3 of admission. The investigations showed a gradual decreasing trend of blood haemoglobin levels along with rising unconjugated hyperbilirubinemia and potassium levels, which remained high despite the administration of Potassium-binding resins. Blood investigations also revealed increased reticulate count and

a positive direct Coombs' test. Because her haemoglobin continued to decrease, she received 2 units of PRBC on the third and fourth days after admission. The thyroxine sodium dose was escalated. She improved within 2 days of starting the conservative management- fever subsided, gum hypertrophy and purpuric spots with bruising started to reduce.

On Day 6 of admission (Figure 3), a Skin biopsy report came- showed tissue with epidermis showing mild eosinophilic spongiosis, superficial dermis shows perivascular and peri-adnexal moderate mixed inflammation, including eosinophils, with IgG deposits on DIF, which is suggestive of DRUG RASH.

Figure 2. Showing bilateral palpable purpura in both lower limbs on Day 6 of admission.

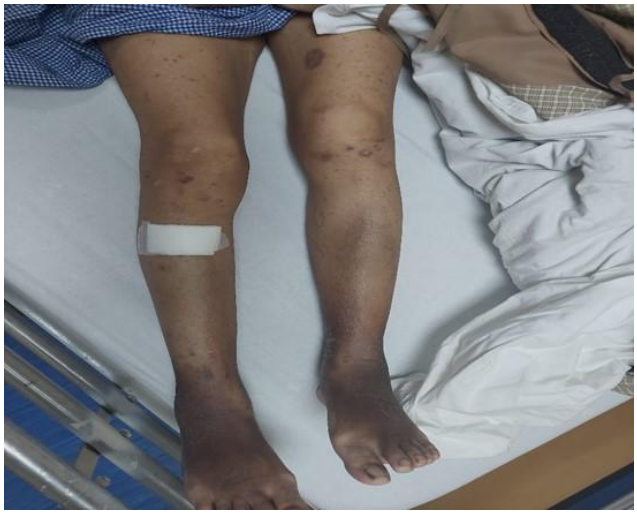
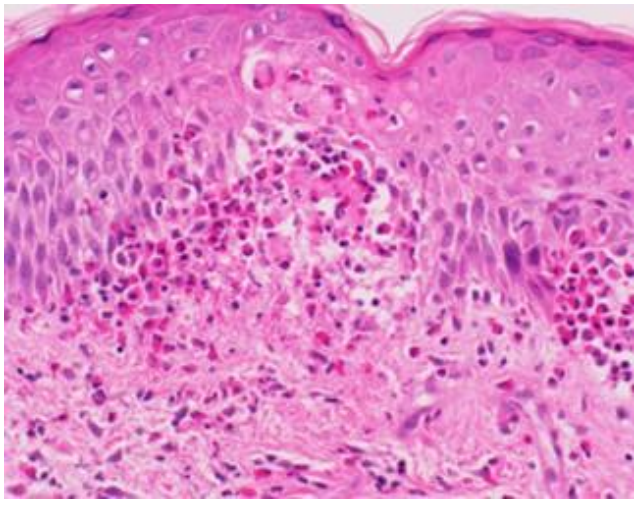


Figure 3. Skin Biopsy showing Eosinophilic infiltrates with inflammation, Suggestive of Drug Rash.



2.1 Differential Diagnosis

Given all clinical and laboratory findings, she was initially diagnosed with adult-onset Henoch-Schonlein Purpura. A similar clinical scenario could be found in any systemic infection, ruled out as all cultures and tropical fever panels were negative. For autoimmune diseases, ANA, ANCA, C3, C4, and Ferritin were tested which all were negative. Haematological malignancies were ruled out by regular monitoring of blood counts and peripheral blood smears. The patient was assessed using the Naranjo algorithm, scoring 6, indicating a probable adverse drug reaction. Key points include improvement of

the reaction after drug discontinuation, no previous conclusive reports, consideration of alternative causes, and confirmation by objective evidence.

2.2 Treatment

Amlodipine was discontinued immediately after admission, and Thyroxine sodium was escalated after initial reports. She was treated conservatively and was initiated on Tablet Bilastine and Tablet Ketotifen after the skin biopsy report. No immunosuppressive agents were given for autoimmune haemolytic anaemia.

2.3 Outcome and Follow-Up

She improved with conservative management. Her fever subsided with the discontinuation of Amlodipine. Gum hypertrophy, skin rash with bruising spots subsided gradually over the next 4 weeks. After 4 weeks of follow-up, her blood parameters of Haemoglobin, Serum bilirubin, Serum Potassium, and Serum albumin were all within normal range.

3. Discussion

The clinical features and laboratory findings were suggestive of adult-onset Henoch-Schnolein Purpura but were later diagnosed as systemic side effects due to amlodipine. Gingival hyperplasia is one of the known side effects of the administration of Tab Amlodipine, following 2 months of its onset, with a reported prevalence of 3.3%. The pathophysiology is still unclear, with proposed inflammatory and non-inflammatory pathways. Discontinuation of the drug and meticulous oral hygiene maintenance by the patient are helpful for a reduction in gingival overgrowth [4]. Madi et al previously had a case report of Amlodipine-induced gingival hypertrophy [5].

Amlodipine-induced abdominal pain is not a common side effect. Probable causes could be dyspepsia, flatulence, constipation, pancreatitis, and rarely intestinal obstruction [6]. Abdominal pain was not evaluated, as it went away as soon as Amlodipine was discontinued. Amlodipine causes drug fever on rare occasions, with an incidence of less than 1% [7]. The possible mechanisms can be Hypersensitivity reactions, Idiosyncratic reactions, as an extension of the pharmacologic effect of a drug, due to failed thermoregulation, due to loss of physiological control mechanism of thermoregulation or associated with drug administration- parenteral administration of certain drugs can directly lead to to to to fever [8].

Palpable purpuric spots and bruising are side effects of the Dihydropyridine Calcium channel blocker Amlodipine, with an incidence of less than 1%. The cause of palpable purpura by amlodipine is to increase in capillary hydrostatic pressure, which selectively relaxes the precapillary sphincter, causing petechial rash and oedema. The addition of ACEI or ARB with Amlodipine can reduce the incidence. This is not a serious adverse effect of Amlodipine, but it can cause aesthetic complaints from the patient. Murthy et al previously reported Amlodipine-induced petechial rash [9]. Knee swelling could also be attributed to the same mechanism.

Immune hemolytic anaemia as an adverse effect of Amlodipine use is very rare and has only been reported during post-marketing reports; the mechanism is unknown [10]. In immune hemolytic anaemia, IgG, immunoglobulin M (IgM), or both bind to antigens on the surface of RBCs and initiate their destruction through the complement and mononuclear phagocytic systems. Immunologic mechanisms can be either drug-dependent, which involves antibody formation against RBCS due to the drug, or independent, which forms antibodies against RBCs in the absence of the drug, which can be seen in vitro [11].

Ketotifen is an H1 receptor antagonist and mast cell stabiliser. Hence, it has antihistaminic and anti-anaphylactic property, which helps in the improvement of symptoms. Although it has not been documented to have proven mortality benefit but can help sig-

nificantly for supportive treatment as was done in our patient [12]. Considering the clinical scenario, the probable pathophysiology of the whole presentation is likely to be a Type II hypersensitivity reaction, which was evidenced by the presence of immune hemolytic anaemia [13]. When we accessed the WHO-VIGIBASE database, we could only find 1 incidence out of the total documented 165641 adverse drug reactions to amlodipine, which has been said to be Type II hypersensitivity reaction [1]. Previous references of similar drug reactions occurring simultaneously in a patient due to Amlodipine use were searched extensively, but we could not come across any similar case report, although separate individual reports have been previously given.

4. Conclusion

A careful and methodical clinical approach, grounded in scientific principles, remains essential in the evaluation and management of any patient. In the present case, although the patient exhibited clinical features consistent with adult-onset Henoch-Schönlein Purpura, a skin biopsy was crucial in establishing the correct diagnosis of Amlodipine-induced multisystemic adverse effects. This case highlights the importance of considering drug-induced etiologies even when the clinical presentation mimics well-known diseases. Notably, the rare combination of adverse effects observed in our patient was confirmed by her complete recovery following the discontinuation of Amlodipine and supportive conservative management, underscoring the reversible nature of such drug-related complications and the value of prompt recognition and intervention.

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Research Ethics Committee Approval: The patient provided written informed consent for participation, and the study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki.

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Conflicts of Interest: All other authors declare no conflicts of interest.

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