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Tramadol Induced Angioedema in a Patient with Systemic Lupus Erythematosus – A Case Report

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Abstract:
Background*: Systemic lupus erythematosus [SLE] is an autoimmune disease which is known to affect several organ systems. Patients with SLE are likely to experience hypersensitivity reactions including angioedema. Angioedema is a life-threatening condition which is accompanied by the swelling of skin and soft tissues of the face, limbs, upper respiratory tract, and gastro intestinal tract. Angioedema is caused by a lack of the C1esterase inhibitor [C1 INH] which leads to hereditary angioedema [HAE]. Acquired angioedema [AAE] is triggered by several drugs, including ACE inhibitors, NSAIDs, and the like. We have reported a case of angioedema within few hours of tramadol intake in a patient with SLE.*
Case summary: *In this case study, we have described a 22 years old female patient who was initially diagnosed with fever, severe joint pains in both knees, vomiting, generalized body pain, throat pain, and difficulty in swallowing for an entire day. She is reported to have a history of systemic lupus erythematosus [SLE]. The patient was treated with an Inj.Tramadol 50mg IV stat for her knee pain as she was experiencing severe pain in the legs. Within 5 hours of administration, she experienced facial swelling and limb swelling. Thereafter, her condition worsened characterised by slurred speech, increased salivation, difficulty in swallowing, and urticaria. Thus, angioedema was suspected and Inj. Tramadol was withdrawn from the patient's treatment. However, other medications remained unchanged*
Keywords*: Systemic lupus erythematosus, auto immune disease, angioedema, tramadol*

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I. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which affects millions of people worldwide every year. SLE is characterized by multi-organ involvement, autoantibody formations, and the dysregulation of the complement system[1]. Patients with SLE are known to have increased susceptibility towards developing an allergic reaction and angioedema is one of the rare manifestations of this disease[2]. Angioedema is a non-pitting, non-pruritic, and painless swelling of the sub-mucosal as well as sub-cutaneous tissues, especially of the face, larynx, lips, tongue, genitals and body extremities[3]. Angioedema is broadly classified into mast cell-mediated and kinin mediated. Kinin mediated angioedema is the hereditary angioedema (HAE), which is caused by the deficiency of the C1 esterase inhibitor (C1 INH). It results in episodes of swelling with variable age of onset of symptoms, usually without triggers. Acquired angioedema (AAE) also exists but it is different from HAE. AAE occurs later in the life, in the absence of family history, due to the presence of anti-C1 INH antibodies in association with lymphoproliferative disorders[4].

Acquired angioedema can be induced by several drugs like anti-hypertensive medications such as angiotensin-converting enzyme inhibitors (ACE), opioid drugs, Nonsteroidal anti-inflammatory drugs (NSAIDs), and oral contraceptives. Additionally, AAE can be associated with kinin mediated initiated angioedema[5]. Tramadol is used frequently as an analgesic in both domiciliary care as well as the hospital settings due to the relatively lesser risk of dependence, drug interactions, and abuse as compared to other opioid analgesics. It is also used as an alternative treatment for osteoarthritis in whom NSAIDs are contraindicated or those with no pain relief in spite of the oral analgesic administration[6]. The exact mechanism behind tramadol induced angioedema is still yet to be found out. In the following section, we have described a patient with SLE who experienced angioedema following tramadol intake[7.]

II. Case Report

A 22 years old female patient arrived in the emergency ward with the primary complaints of fever, which was of a high-grade continuous type characterised by chills and rigors; vomiting, generalized body pain, knee pain, and throat pain for an entire day. The patient was already known to have a history of SLE and was on a number of medications which included T. Hydroxychloroquine 200mg OD, T. Folic acid 5mg OD, T.Calcium carbonate 500 mg OD, T.Ferrous fumarate OD, and T.Azathioprine 500mg OD. The patient did not have any significant history of drug allergy. She , however did report a past history of allergy to chicken. Bowel and bladder habits were reported normal and her menstrual cycles were regular without any change.

On general examination, the patient was observed to be conscious, oriented, and febrile. On physical examination, the patient's temperature was found to be 102.4°F, pulse -102/min, CBG-91mg/dl, BP-120/80 mm/hg, respiratory rate-22/min, SPO_2-98.2% under room temperature. CVS-S1S2(+), RS- bilateral air entry (+), Abdomen- soft, CNS- Non-Focal Neurological Deficit. The patient was first treated with supportive medication such as intravenous fluids 75ml/hr, Inj. Paracetamol 1gm IV TDS, Inj. Ondansetron 4mg IV BD, and T. Hydroxychloroquine 200mg BD at the time of admission, which was in the early hours of the morning (1 AM). Within a few hours, the patient experienced progressively worsening bilateral knee and leg pain. She was given Inj. Tramadol 50mg IV stat. Within 5 hours, the patient displayed facial swelling, upper limb swelling, difficulty in swallowing, and severe body ache. She was treated with Inj. Hydrocortisone 200mg IV Stat, Inj. Chlorpheniramine 2cc IV Stat, Inj. Furosemide 20mg IV Stat, T.Calcium 500mg OD, T.Pregabalin HS, Inj.Pentazocine, and Inj.Promethazine IM Stat. Inj.Tramadol drug was withdrawn. Inj.Ketorolac 30 mg IV slow stat was given for pain.

At 3 PM, on the following day, the angioedema worsened. Several symptoms including slurred speech with increased salivation, facial swelling, difficulty in swallowing, and urticaria were observed. The patient was administered with Inj.Piperacillin + Tazobactum 4.5mg IV TDS and immediately shifted to the ICU. The patient was managed with Inj. Chlorpheniramine 1amp IV TDS and Inj. Adrenaline 1:10000 3cc IV Stat in ICU and her vitals were monitored at continuous rate.T.Azithromycin 500mg OD, T.Cetirizine 1 tab HS were added.

Diagnostic tests like Hb:10.4 g%, (normal-12.0-15.5g%), WBC: 5500 m/mm3 (normal-4500-11000m/mm3), Neutrophils-68 (normal-40-60%), Lymphocytes-28 (normal-20-40%), Platelets:187 (normal-150-450×109/L) ESR: 15 (normal- 20mm/hr), Urea: 19 (normal- 5-20mg/dl), serum creatinine: 0.7 (normal-0.6-1.2mg/dl), bilirubin total: 0.5 (normal-0.1-1.2mg/dl), bilirubin direct: 0.2 (normal-<0.3mg/dl), total protein: 6.5 (normal-6-8.3g/dl), albumin:3.0 (normal-3.4-5.4g/dl), globulin:3.5 (normal-2.0-3.5g/dl), SGOT: 15 (normal-5-40IU/l), SGPT:14 (normal-7-56IU/l), ALP: 72 (normal-44-147IU/l), Uric acid: 2.9 (normal-2.4-6.0mg/dl). Urine PCR, C3, C4, dsDNA, Chest X Ray, blood culture, urine culture, CRP, ESR were within normal limits. After 12 hours of administration of Inj.Chlorpheneramine and Inj.Adrenaline, the angioedema subsided.

A video laryngoscopy showed tongue-bulky and the occurrence of candid plaque over the surface of the tongue. Bilateral vocal cordomoids and arytonoids were observed to be normal. The Otorhinolaryngologist advised to continue with the course of steroids. The patient was placed under observation for 24 hours in the ICU following which, the patient's condition improved and she was shifted to the general ward by stopping Inj. Hydrocortisone 200mg on (day2).

The final diagnosis was SLE with arthralgic flare and angioedema was due to possible tramadol use. After 8 days of hospital care and management with a course of steroids, antibiotics and other supportive treatment, she was discharged. The medications prescribed during her discharge were T.Prednisolone 30mgOD, T.calcium-vitamin D3 OD, T.Paracetamol 750mg BD, T.Hydroxychloroquine 200mg BD, octyl methoxycinnamate and oxybenzone, titanium dioxide L/A.

III. Discussion

To the best of our knowledge, this is the first case study on the association of angioedema induced by tramadol in patient with SLE. SLE is a chronic inflammatory disease which occurs in approximately 70 out of 100,000 people[5]. A cross-sectional study of total 90,485 hospitalizations in New York revealed that patients with SLE had a higher chance of developing angioedema. A total of 1505 patients among them had both SLE and angioedema[1]. Lahiri M, *et al*, described angioedema as the initial presenting feature in a 53-year old Chinese woman, who was subsequently diagnosed to have SLE on the basis of laboratory investigations. She had facial swelling as well as limb swelling and the angioedema was subsequently severe enough to result in respiratory compromise[4].

Angioedema is known to occur with drugs such as ACE inhibitors, beta lactam antibiotics, NSAIDs, and the like. Tramadol is also reported to cause angioedema as an adverse event although the literature on this is very sparse. The case of tramadol induced angioedema is reported to vary between 1 in 1000 to 1 in 10000[8]. Angioedema may be allergic or non-allergic in origin. The differences between allergic and non-allergic angioedema are highlighted above. Since our patient reported the reaction just after 5 hours of drug intake, it is

likely to be non-allergic in origin and mediated by the bradykinin system. The lack of family history of angioedema almost precludes a diagnosis of hereditary angioedema caused by the C1-INH deficiency[9].

Kaya *et al*, have demonstrated in an in vitro study on rabbit aorta rings that tramadol induces relaxation of the vascular smooth muscle through the activation of the nitric oxide synthase- guanylate cyclase pathway. It may also have a direct effect on the vascular smooth muscle independent of the endothelium effect[10]. Besides this, tramadol also plays a key role in inhibiting serotonin reuptake, which increases serotonin levels. The rise in serotonin levels can increase NO production which aggravates the vasodilation[11].

In our case report, the patient had primary complaints of fever, vomiting, throat pain, dysphagia, multiple joint pains, and generalized body ache since the first day and was admitted to the hospital. The patient was already known to have a previous history of SLE, and thus, was kept on medications. The patient was administered with Inj. Tramadol 50mg IV for her primary complaints of severe leg pains. After few hours she developed angioedema. The patient was supported with steroids, antihistamines, and other supportive measures. The patient was discharged after 7 days.

Analysis of the reaction for causality as per Naranjo's algorithm showed this to be a "possible cause" as dechallenging did not show immediate remarkable progress while rechallenging was not possible owing to ethical reasons. However, there is a strong pharmacological plausibility of opioids causing the angioedema. Additionally, the temporal relationship between the reaction and the drug intake makes one to conclude that there is a reasonable plausibility for tramadol to be the offender in this scenario. The patient was advised to avoid opioid drugs. Her recovery was uneventful without any sequelae. She was asked to continue her regular medication for SLE.

IV. Conclusion

Patients with SLE can develop angioedema due to opioids such as tramadol. Physicians and patients must be aware of this rare life-threatening reaction to opioids. Therefore, it is important to notify the drug monitoring centres about the occurrences of this serious and unpredictable adverse effect of tramadol.

References

[1]. Yiming LU, Xiaowen FA, et al. Systemic Lupus Erythematosus and Angioedema: A Cross-Sectional Study from the National Inpatient Sample. Archives of rheumatology. 2019 Jun;34(3):301.
[2]. Couture J, Ben- Shoshan M, et al. Risk of allergic conditions in children born to women with systemic lupus erythematosus. Arthritis care & research. 2018 Feb;70(2):315-9.
[3]. Michailidou D, Kribis M, et al. Facial and limb angioedema with parotitis and Kikuchi-like necrotizing lymphadenitis preceding neuropsychiatric systemic lupus erythematosus in a young African American male. Lupus. 2018;27(4):676-80.
[4]. Lahiri M, Lim AY. Angioedema and systemic lupus erythematosus--a complementary association? Annals-Academy Of Medicine Singapore. 2007 Feb 1;36(2):142..
[5]. Bienstock D, Mandel L. Facial angioedema and systemic lupus erythematosus: case report. Journal of Oral and Maxillofacial Surgery. 2015 May 1;73(5):928-32.
[6]. Mehrpour O, Sharifi M, Zamani N. Tramadol poisoning. Toxicology Studies: Cells, Drugs and Environment. 2015;8:101.
[7]. Hallberg P, Brenning G. Angioedema induced by tramadol—a potentially life-threatening condition. European journal of clinical pharmacology. 2005;60(12):901-3.
[8]. Grassmann C. An unusual adverse reaction to tramadol. Anaesthesia. 2008;63(4):442-.
[9]. Habibagahi Z, RuzbehJ, et al. Refractory angioedema in a patient with systemic lupus erythematosus. Iranian journal of medical sciences. 2015;40(4):372.
[10]. Kaya T, Gursoy S, et al. High-concentration tramadol-induced vasodilation in rabbit aorta is mediated by both endothelium-dependent and-independent mechanisms. Acta PharmacologicaSinica. 2003;24(5):385-9.
[11]. Desmeules JA. The tramadol option. European Journal of Pain (London, England). 2000;4:15-21.

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