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RESEARCH ARTICLE

ACETAMINOPHENINDUCED LEUCOCYTOCLASTIC VASCULITIS WITH EROSIVE GASTRITIS

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ABSTRACT

Background: Acetaminophen is a non-steroidal anti-inflammatory drug (NSAID) widely used for its analgesic and antipyretic properties. Although it is relatively very safe, it has been associated with hepatotoxicity and other minor gastrointestinal adverse effects. In addition, it has also been reported that some NSAIDs can cause severe cutaneous adverse effects such as leucocytoclastic vasculitis (LCV).

Case description: A 35 yearold female patient was admitted intointensive care unit (ICU) with multiple palpable purpura discretely located bilaterally all over the upper and lower limbs. Prior to its onset, the patient had an episode of severe headache and body pains for which she consumed over the counter (OTC) acetaminophen. The lesions worsened abruptly and a skin biopsy confirmed the presence of leucocytoclastic vasculitis. The patient also had a clinical evidence of erosive gastritis. The offending agent was immediately discontinued and the patient was successfully managed with corticosteroids and supportive therapy. However, the patient was not re-challenged with acetaminophen owing to severity of the reaction as well as for ethical reasons.

Discussion and evaluation: An extensive review of the current case reveals the occurrence of erosive gastritis and LCV following the over the counter (OTC) use of acetaminophen. A thorough evaluation of patient's clinical history, physical examination, laboratory and histological examination, confirmed acetaminophen induced LCV along with erosive gastritis. The present adverse drug reaction was classified as probable with a score of 6according to Naranjo's scale causality assessment and is classified severe (level 5) according to Hartwig's scale of severity assessment. Drug induced LCV is an extremely rare reaction. Although it has been reported with a few NSAIDs such as naproxen and Ibuprofen, to best of our knowledge, acetaminophen has never been associated with LCV. The case is also unique in its presentation of LCV occurring concurrently with erosive gastritis in the same patient.

Conclusion: Acetaminophen is the most commonly used OTC drug worldwide. Despite its established safety, it can produce serious adverse effect such as leucocytoclastic vasculitis. Early diagnosis and drug with drawl are crucial to the resolution of the leucocytoclastic vasculitis.

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INTRODUCTION

Currently, non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used agents for their analgesic, antipyretic and inflammatory properties (Hyder *et al*., 2012). They are indicated in the treatment of headaches, toothaches, muscle pain, back pain, arthritis, cold and fever. Among all NSAIDs available, acetaminophen is the most frequentlyadministered. Apart from being available over the counter, it is safe and effective for all ages. It is a weak inhibitor of prostaglandins (PGs) synthesis and thus possessing weak anti-inflammatory properties (Graham *et al*., 2005). In general, acetaminophen is well tolerated with lower incidence of adverse drug reactions. Leucocytoclastic vasculitis (LCV) or hypersensitivity vasculitisis an extreme reaction to a drug, infection, systemic diseases or malignancy (Fett, 2016). It causes inflammation and damage to blood vessels resulting in thickening, weakening, narrowing and scarring of vessels. Rarely, infections of upper respiratory tract particularly beta hemolytic streptococci,

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HIV infections, bacterial endocarditis and hepatitis C have been associated with LCV. Most potential drugs involved in causing LCV are antibiotics (particularly beta lactams), NSAIDs and diuretics. Although the exact pathogenesis remains unclear, it has been illustrated that circulating immune complexes are often involved (A Brooke, 2016). Typically, it presents with symptoms of arthralgia, myalgia and skin rashes. Bowel involvement may cause symptoms like abdominal pain and diarrhea. Early withdrawal of the offending drug usually leads to complete recovery while more advanced disease and late withdrawal of the drug may necessitate the use of immunosuppressive therapy (Mislav Radić, 2011). Here, we report a rare case of leukocytoclastic vasculitis with erosive gastritis resulting from the over the counter use of acetaminophen.

CASE REPORT

A 35 year old female patient presented to the emergency department with chief complains of progressively worsening pruritic rashes over the lower limbs, radiating to the trunk and upper limbs for 18 days. The patient also complained of abdominal pain in the fundal region. On further interviewing the patient for her condition, she revealed that the rashes developed immediately following the use of acetaminophen which she said consumed for her headache and back pain a few days ago. The patient also had a history of 6 episodes of vomiting (non-projectile and watery in consistency), melena and sore throat prior to admission.

The patient had past medical history of chronic diseases for which she was receiving following medications:

Tab Met-XL (Metoprolol) - 12.5 mg for hypertension
Tab. Thyronorm (Thyroxine)- 50 mcg for hypothyroidism
Tab. Sod. Valproate – 200 mg for epilepsy

Patient also had a past history of inguinal hernia for which she had undergone bariatric surgery 4 years back. There was noprevious history of photosensitivity, genital or oral ulcers or allergic reactions to any drugs. Further, patient denied consuming any herbal or dietary supplements.

On admission, the patient's vitals were:

Temperature-98°F,
B.P: 160/80 mm Hg,
Pulse: 96 beats/min,
Respiratory rate: 22 beats/min.

A complete clinical examination of her lower extremities revealed multiple palpable purpura discretely located over bilateral upper and lower limbs with minimal trunk involvement. Numerous red spots (1-2mm) or petechiae over both the lower and upper extremities were present. Chest, cardiovascular and joint examination were normal. All the rest physical examination was normal except for mild tenderness in the epigastric region. Hematological analysis revealed leukocytes is with other parameters being completely normal (Table 1).

Table 1. Laboratory reports

LABORATORY PARAMETERS (units)	REPORTS		REFERENCE VALUES
	On Admission	At Discharge	
COMPLETE BLOOD PICTURE			
Haemoglobin (gm/dL)	12	14.2	11.5 - 17.0
Mean Corpuscular Haemoglobin concentration (g/dL)	31.8	33.6	32.0- 36.0
Total Leukocytic count (x 103/mm3)	20.7	9.8	4.0 - 10.0
Differential leukocytic count (%)			
Neutrophil	92.7	65.4	50.0 – 80.0
Lymphocyte	25.8	32.8	25.0 – 50.0
Eosinophil	1.3	2.0	0.00 – 0.50
Basophil	0.02	0.03	0.00 – 0.20
Platelet count (x 103 mm3)	375	410	150 – 500
LIVER FUNCTION TEST			
Bilirubin (mg/dL)			
Total	0.8	0.7	0.2-0.8
Direct	0.2	0.2	Upto 0.2
ALT (U/L)	15	20	5 – 45
AST (U/L)	17	22	5 – 45
Alkaline phosphatase (IU/L)	125	80	28-88
Protein, total (g/dL)	7.2	7.0	6.0-7.5
Albumin (g/dL)	4.5	4.8	3.5- 5.0
Globulin (g/dL)	0.8	0.6	0.2- 0.8
COAGULATION PROFILE			
Prothrombin time (s)	18	13	13-15
INR	1.5	1.4	1.3
RENAL PROFILE			
Serum Creatinine (mg/dL)	0.7	0.8	0.6-1.5
Blood urea (mg/Dl)	27	30	10-45
Sodium (meq/L)	135	138	135-145
Potassium (meq/L)	4.6	4.2	3.5-5.0
Chloride (meq/L)	95	98	95-105
URINE ANALYSIS		Not done	
Colour and appearance	Light red & clear		
Specific gravity	1.005		
Albumin	Traces		
Sugar	NIL		
Pus Cells (/HPF)	2-3		1-2
RBCs (/ HPF)	NIL		NIL
Epithelial Cells (/ HPF)	3-4		1-2
Anti-nuclear antibody	Negative	Not done	
Rheumatoid factor	Negative	Not done	

Table 2. Naranjo Adverse Drug Reaction Probability Scale (Srinivasan, 2011)

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
	Total Score:6			

Table 3. Hartwig's Severity Assessment Scale (Srinivasan, 2011)

LEVEL 1	An ADR occurred but required no change in treatment with the suspected drug.
LEVEL 2	An ADR required that the treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
LEVEL 3	The ADR required that the treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An antidote or other treatment was required. No increase in length of stay (LOS).
LEVEL 4	Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was reason for the admission.
LEVEL 5	Any level 4 ADR which requires intensive medical care.
LEVEL 6	The adverse reaction caused permanent harm to the patient.
LEVEL 7	The adverse reaction either directly or indirectly led to the death of the patient.

Mild = Level 1,2; Moderate = Level 3,4; Severe = Level 5,6,7.

Other biochemical parameters like serum electrolytes, serum creatinine and blood glucose were normal. Except for a slight increase in alkaline phosphatase (125U/L), the other liver function parameters were normal. Urine analysis showed light red colored urine with a few pus cells (2-3/HPF) and epithelial cells (3-4/HPF). Coagulation profile was altered (Prothrombin time-18sec, PP:1.38, INR:1.5) whereas antinuclear antibody(ANA) and rheumatoid factor (RF) were negative The viral markers for HIV and hepatitis-B w.

Biopsy: Features suggestive of Leukocytoclastic Vasculitis.

Upper G.I Endoscopy: Fundal and Antral Erosive Gastritis.

A skin biopsy was performed using 2 skin biopsy pieces each measuring 0.3 cm. A histological examination of the skin showed epidermis with mild hyperkeratosis, moderately dense perivascular infiltrate of lymphocytic cells and plenty of neutrophils in dermis along with focal infiltration and few fragmented neutrophils into the vessel wall. These features were consistent with leucocytoclastic vasculitis. Based on the clinical history of acetaminophen intake preceding the development of LCV and gastritis as well as lack of any other underlying etiology; a diagnosis of acetaminophen induced leucocytoclastic vasculitis with erosive gastritis was made.

The patient was appropriately managed with corticosteroids, anti-ulceratives and antacids. A 6 day course of IV steroid (Hydrocortisone- 50mg-IV- TID) followed by topical steroids (Mometasone- 0.1% w/w- TID) were given. Gradual improvement with the disappearance of the skin lesion on the lower extremities was seen on the third day. Anti ulcerants {Pantoprazole (40mg-IV-BD), Sucralfate (1ml- TID)} were administered to prevent further damage to GI mucosa and to heal the underlying ulcers.

The patient was effectively counseled to restrict further use of NSAIDs to prevent further damage and to prevent the potential cross reaction with other agents. The rashes gradually disappeared on the 6th day and she was discharged on the 7th day. At follow up after a month, the patient was doing well with significant improvement of her upper and lower extremities.

DICUSSION

Acetaminophen is among the safest drugs to be available over the counter. However, in the present case, it lead to a potentially severe cutaneous reaction-leucocytoclastic vasculitis with erosive gastritis. Drug induced LCV can be determined based on 5 defining characteristics: 1) Age greater than sixteen years, 2) Palpable purpura, 3) A maculopapular rash 4) A skin biopsy revealing infiltration of WBCs around an arteriole or venule. 5) A temporal relation of symptoms and usage of probable precipitating drug (Calabrese *et al*., 1990). In our case, 4 out of 5 criteria are satisfied simulating drug induced LCV. The patient also had clinical evidence of gastritis which was later confirmed with gastrointestinal endoscopy. Based on drug induced LCV criteria together with clinical evidence of erosive gastritis as well as closely associated history acetaminophen intake preceding the development of the reaction, a diagnosis of acetaminophen induced LCV with erosive gastritis was apparent. On Naranjo's scale of causality assessment the adverse effect is classified as probable with a score of 6. (Table 2). On Hartwig's Severity Assessment Scale, the reaction is at level 5 which is classified as severe (Table 3).

Conclusion

Although Acetaminophen is considered to be a safe NSAID when used in therapeutic doses, it can produce serious adverse

effects such as LCV. Early recognition and withdrawal of the offending drug is essential to prevent further complications. As it is the most widely used over the counter drug, awareness regarding its rare adverse effect is necessary.

Abbreviations

NSAID: non-steroidal anti-inflammatory drug; ADR: adverse drug reactions; LCV: leukocytoclastic vasculitis; ANA: anti-nuclear antibody; HSV: hypersensitivity vasculitis, RA: rheumatoid Factor, LOS: lengthof stay.

Compliance with ethical guidelines

Conflict of interests: The authors declare that they have no conflictof interests.

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