A CASE STUDY

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

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Abstract: This case study describes an incidence of a Drug Reaction with Eosinophilia and Systemic Symptoms or DRESS secondary to Phenytoin. DRESS, characterized by pyrexia, diffuse maculopapular rash, eosinophilia with reactive lymphocytes, hepatitis and renal dysfunction. Similar cases are seen in some variation in clinical settings where Physician Assistants are employed and carry a high degree of mortality. Through the review of this case the Physician Assistants will improve familiarity with the signs, symptoms, diagnosis and treatment of DRESS, as well as the significant associated mortality and common offending medications.

Introduction to the Scenario

Pre-admission Course

A 27-year-old male sustained two generalized tonic-clonic seizures on April 28th after a night of alcohol use and was prescribed a Phenytoin intravenous load upon presentation to the emergency department. The Phenytoin level post-loading dose was therapeutic at 15.1 micrograms/L, and the patient was discharged from the department on oral therapy of Phenytoin at 100 mg orally dosed three times daily. The follow-up with his family physician on May 7, indicated elevated liver enzymes of AST 207 and ALT 145 U/L. Phenytoin level was noted to be supratherapeutic at 26 micrograms/L one week later, and phenytoin dosage reduced. Other labs were unremarkable, with normal values of cholestatic enzymes, bilirubin; white blood cell count was also normal. A Urinalysis was also bland – having no casts/leukocytes, or erythrocytes present. The patient followed up with their family physician again three weeks later on May 28, and a repeat phenytoin level also remained supratherapeutic with a level of 25; no liver enzymes were reported at this time. Two days later (May 30), he was prescribed Prednisone at 50 mg/daily for seven days for a maculopapular rash. However, he did not notice substantial improvement and phenytoin was continued. Due to ongoing symptoms, he subsequently stopped the Phenytoin on June 3rd.

Hospital Admission

On June 5, the patient presented to the Emergency Department with an ongoing progressive maculopapular rash, lethargy, pyrexia accompanied by chills, myalgias, arthralgias and nausea

and vomiting. On exam, vital signs revealed pyrexia with a temperature of 38.7. The patient was awake, alert, and oriented x 3, non-toxic in appearance. Progressive maculopapular, non-pruritic rash of >50% body surface area was noted primarily involving lower extremities, and patchy distribution to the upper body including left wrist, right arm, and some facial involvement. Lips were excoriated with no other mucosal involvement. Cardiac exam revealed no murmurs. Air entry was clear bilaterally on auscultation with no adventitia. Bowel sounds were present, abdomen was soft and diffusely tender, primarily over the right upper quadrant to palpation with no rebound tenderness. Assessment for lymphadenopathy was not documented.

Medical history was significant for a prior seizure in 2010 for which the cause was likely alcohol-related. There were no known allergies. Surgical history included a remote mandibular surgery 20 years prior. A history of sporadic smoking was obtained, with heavy alcohol use (often upwards of 6 drinks per sitting) in the past although cessation of alcohol had occurred since the most recent seizure. Current medications were only Prednisone which was completed on the day of presentation to the hospital; Phenytoin had been stopped on June 3rd.

Investigations revealed leukocytosis with WBC elevation of 20.1 with reactive lymphocytes and eosinophilia; absolute eosinophils were elevated at 0.86 initially and peaked at 6.79 (31.7%). Bilirubin remained normal, however, both cholestatic and hepatocellular liver enzymes were elevated (AST 57, ALT 273, LD 278, GGT 487, Alk Phos 228), as were BUN (11.6) and Cr (210). Dilantin level was subtherapeutic at 3.7. Salicylate level was negative. Repeat urinalysis revealed 1-2 RBC/WBC per hpf, 1-2 hyaline/granular casts. Chest XRay showed clear lungs with no pleural abnormality, urine culture revealed normal urogenital flora.

Course of Care

Phenytoin had been discontinued prior to admission, and Internal Medicine was consulted from the Emergency Department and continued to follow throughout admission and upon discharge. Differentials were Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis or Erythema Migrans; with DRESS being considered most likely given the relative sparing of mucous membranes, lack of blistering rash and the later onset of symptoms at 4 weeks. Renal function peaked with a Creatinine of 279 two days post admission and Prednisone 50 mg/daily was started at this time. Progressive maculopapular rash continued for several days and appeared to stabilize, but did not subside. Pyrexia was ongoing, and peaked at 39.2 two days post-admission; subsequently, the patient remained afebrile after this time and blood cultures on at least 2 separate occasions were negative. Hepatitis markers appeared to peak on day five post admission and continued throughout hospitalization; eosinophilia and reactive lymphocytes also continued to be present. Hepatitis B &C serology returned negative results.

Despite medical concerns, the patient was insistent upon discharge and was subsequently discharged home seven days post-admission with family physician and Internal Medicine follow

up. On discharge, Prednisone was continued with a progressive tapering of the dose by 10 mg weekly until a dose of 10 mg daily was achieved and then subsequently discontinued. Renal function at this time had progressively improved with a Creatinine on of 97. Follow-up with the family physician two days post discharge occurred and repeat labs which demonstrated improving hepatitis, ongoing leukocytosis, and essentially resolved eosinophilia. Further patient outcomes, follow-up, and treatment response is otherwise unknown.

Discussion

Phenytoin, a hydantoin anticonvulsant is indicated for the treatment of generalized tonic clonic seizures, as well as complex partial seizures. It undergoes hepatic metabolism and possesses zero-order pharmacokinetics which makes dose-related toxicity a concern.[1] While often well tolerated, it is known to occasionally produce severe, even lethal reactions - including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Case reports describing a "pseudolymphoma" related to Phenytoin with accompanying symptoms of fever, lymphadenopathy, eosinophilia, hepatosplenomegaly and exanthema were first described in 1959 by Saltzstein & Ackerman. [2] Additionally, in 1961 Siegal and Berkowitz[3] described hypersensitivity to Phenytoin with mononucleosis-like symptoms illness accompanied by fever, jaundice, atypical lymphocytosis, lymphadenopathy, rash, and hepatic injury which improved upon discontinuation of the drug, but reappeared within hours of taking a single test dose of Phenytoin (Dilantin).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

While known by a variety of names (drug-induced hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome, drug-induced delayed multiorgan hypersensitivity), the drug reaction with eosinophilia and systemic symptoms (DRESS) acronym was first put forth by Bocquet et al. who proposed the criteria for diagnosis as including skin eruption, eosinophilia or atypical lymphocytes and internal organ involvement. DRESS is an uncommon but potentially lethal hypersensitivity reaction to medication, frequently antiepileptics. Estimated DRESS risk at first or second prescription of an aromatic antiepileptic drug is 2.3-4.5/10,000.[4] Mortality rate is widely quoted as approximately 10%, most commonly secondary to liver failure. Symptoms vary, making diagnosis challenging, however a widely seen pattern begins with fever, followed by a maculopapular rash shortly thereafter, and subsequently the involvement of internal organs including interstitial nephritis, myocarditis, pneumonitis, and on rare occasions meningoencephalitis.[5] The type of rash seen and internal organ involvement are variable; there has been no pathognomonic rash identified for diagnosis.

Pathogenesis is incompletely understood, but likely involves an interplay between several factors. Drug-specific T cells are the driving force behind this syndrome. [6] Different mechanisms have been implicated in its development, including detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation, and reactivation of human herpes viruses, including Epstein-Barr virus and human herpesvirus (HHV 6 and 7) [7] as well as a

possible ethnic genetic predisposition with some HLA alleles. Sequential herpesvirus reactivations observed in DIHS/DRESS is quite similar to that observed in graft versus host disease (GVHD). The highly variable waxing and waning nature of the clinical manifestations occurring in different organs despite discontinuation of the offending drug could be explained by sequential reactivations of these herpesviruses– nevertheless, sequential reactivation of these viruses were not always associated with evidence of overt clinical symptoms.[6]

Diagnosis

DRESS remains a diagnosis by exclusion, and there is presently no "gold standard" in place for diagnosis. The diagnosis should be suspected based on the initiation of a new drug in the prior two to six weeks, as well as accompanying symptoms of fever, skin rash, lymphadenopathy, and eosinophilia/atypical lymphocytes. Presently, three proposed diagnostic criteria currently exist which vary in ease of use and can complicate as well as delay diagnosis. All criteria include skin rash, eosinophilia/atypical lymphocytes, and internal organ involvement (lymphadenopathy, liver, kidney, lungs, heart) – other criteria proposed for diagnosis include fever, human herpesvirus (HHV) 6 reactivation, thrombocytopenia, and symptoms which persist 2 weeks after discontinuation of the offending drug.

Bocquet criteria require the following 3 features for diagnosis: 1) skin eruption 2) blood eosinophilia (>1.5 x 10^9/L) or the presence of atypical lymphocytes 3) internal organ involvement - including lymphadenopathies (>2 cm in diameter), hepatitis (liver transaminases values >twice the normal upper limit), interstitial nephritis, and interstitial pneumonia or carditis. Other criteria by a Japanese consensus group to diagnose DIHS include: 1) maculopapular rash developing >3 weeks after starting a limited number of drugs, 2) prolonged clinical symptoms 2 weeks after discontinuing the causative drug, 3) fever (>39°C), 4) elevation of liver enzyme (ALT >100) or involvement of other organs, 5) leukocytosis (>11 x 10^3), atypical lymphocytosis (>5%) or eosinophilia (>1.5 x 10^3) 6) lymphadnopathy, and 7) human herpesvirus (HHV)-6 reactivation - diagnosis of typical DIHS requires presence of all 7 criteria. RegiSCAR criteria include at least 3 of the following 7: 1) skin eruption, 2) fever (>38°C), 3) lymphadenopathy at least 2 sites 4) involvement of at least 1 internal organ, 5) lymphocytosis (>4 x 10^3/μL) or lymphocytopenia (<1.5 x 10^3/μL), 6) blood eosinophilia (>10% or 700/μL), and 7) thrombocytopenia (<120 x 10^3/μL) - patients are then classified into definite, probable, possible or no cases according to the scoring system.

The time from drug exposure to onset of symptoms can range from 2-8 weeks, which aids in differentiating DRESS from other skin reactions secondary to medications, such as SJS/TENS which occurs earlier, within 1-3 weeks. Also, most erythematous macules show no evolution into blistering; no mucous membrane involvement is usually seen, which also aids in differentiating DRESS from SJS/TENS.[8] The number of drugs known to induce DRESS is as high as 50 with the most common drugs including carbamazepine, allopurinol, sulfasalazine, phenobarbital, and lamotrigine; numerous antibiotics have also been identified.[7]

Genetic factors have been proposed as being associated with an increased risk of developing severe phenytoin related cutaneous adverse reactions. An association between CYP2C9*3 and decreased clearance of plasma phenytoin, shown to be statistically significant in Taiwan, Japan, and Malaysia populations (an essential genetic factor associated with phenytoin-related severe cutaneous adverse reactions).[9] Other studies have found that certain HLA (particularly HLA-B*56-02) were significantly associated with severe cutaneous adverse reactions related to phenytoin, however, found no significant association between CYP2C9*3 and DRESS, nor did they find any significant association with HLA-B*15:02.[10] In addition to CYP2C9*3, decreased clearance of plasma phenytoin has also been detected in patients with severe cutaneous adverse reactions with HLA-B*-1502 to a lesser degree.[1] Carbamazepine, which shares a similar chemical structure with phenytoin, includes a manufacturer label recommending screening patients of Asian descent for the HLA-B*1502 allele prior to initiating therapy, but presently is not included in the manufacturer labelling of Phenytoin.[11]

Clinical Course

The clinical course is variable; paradoxically, symptoms prolong for several weeks even after stopping the culprit drug; additionally, the duration of symptoms does not appear to differ according to the culprit drug. It has also been demonstrated that relapse is possible with repeat exposure to the offending drug and may also occur when steroids are tapered or discontinued abruptly. Studies have identified prognostic factors in fatal vs. non-fatal cases, with fatal examples demonstrating a higher serum creatinine and ferritin as compared to non-fatal cases; additionally non fatal cases have shown that the duration of symptoms correlated with WBC count, lymphocyte count and tended to be related to eosinophil count in non fatal cases.[12] Mean time for recovery was 6.4+/-9.4 weeks (range 0.5-90 weeks) – no significant differences were found for demographic, clinical, and outcome parameters between cases resulting in death and those that resolved.[7] A marked decrease in serum immunoglobulin levels is typically observed in the acute stage, although their levels eventually return to normal upon recovery.[8] There were also various infections noted in the corticosteroid treatment group in the acute phase (<6 months) – including herpes simplex, herpes zoster, P. *jirovecii* pneumonia, and CMV diseases – most appeared within three weeks and coincided with a tapering of their corticosteroid dose.[8]

Treatment

There have been no evidence-based guidelines for the management of DRESS.
Withdrawal of the offending drug should occur immediately. Treatment with corticosteroids (Prednisone 40-60 mg/daily) is controversial, however typically has been used for at least 6 weeks and has shown dramatic improvement in clinical symptoms and lab findings shortly after initiation in case reports.[13] However, one retrospective study showed corticosteroid use did not significantly affect both recoveries from liver injury or mortality.[14] Spontaneous resolution in minor cases may occur over several weeks; additionally, paradoxical worsening of clinical symptoms often occurs 3-4 days after withdrawal of the causative drug, unnecessary empirical

antibiotic therapy may be started, thereby increasing the risk of developing addition sensitization to these drugs.[8]

Patients with DRESS often show unexplained cross-reactivity to multiple drugs with different chemical structures, including NSAIDS.[8] Lee et al. [14] reviewed 91 cases with DRESS in Taiwan – patients treated with systemic corticosteroids lived longer than those not treated with CS (average 36.3 vs 12.7 days). Plasma exchange and high dose IVIG has been shown to be useful for the treatment of SJS/TEN, but may have adverse consequences in DRESS. The addition of new medications should be avoided when possible to prevent cross-reactivity and clouding of the clinical picture.

Summary

In summary, this case study describes an incidence of DRESS secondary to Phenytoin characterized by pyrexia, diffuse maculopapular rash, eosinophilia with reactive lymphocytes, hepatitis and renal dysfunction. Symptoms associated with DRESS typically have a later onset which helps differentiate DRESS from other potential diagnoses, and symptoms usually persist for several weeks despite discontinuation of the offending medication. Multiple proposed diagnostic criteria can complicate and confuse the diagnosis, leading to a delay in treatment. Despite the lack of randomized controlled trials, the mainstay of treatment involves removal of the offending drug and often therapy with corticosteroids.

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