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CASE REPORT

"DRESSed" to kill: fatal case report of drug rash with eosinophilia and systemic symptoms

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Abstract - Multiorgan dysfunction syndrome (MODS) is a frequently encountered complication in patients who are admitted to the Intensive Care Unit with severe sepsis. Infrequently the same clinical syndrome can be caused by another pathophysiologic mechanism. We present a patient with possible Drug Rash, Eosinophilia and Systemic Symptoms (DRESS). This rare syndrome is caused by an allergic reaction to drugs. Treatment consists of discontinuation of the drug and supportive treatment. Early recognition of DRESS is vital to enable initiation of treatment at an early stage.

Keywords - **DRESS, eosinophilia, drug rash, fever, skin rash.**

Introduction

Multiorgan dysfunction syndrome (MODS) is a frequently encountered complication in patients who are admitted to the Intensive Care Unit with severe sepsis. According to the sepsis campaign guideline, treatment is aimed at a rapid identification of the source of infection, appropriate empiric antibiotics and early goal directed hemodynamic therapy [1]. Infrequently the same clinical syndrome can be caused by another pathophysiologic mechanism. In this case report we present a patient with possible Drug Rash, Eosinophilia and Systemic Symptoms (DRESS). This rare syndrome is caused by an allergic reaction to drugs. The clinical features and possible therapeutic options of this syndrome are described.

Case presentation

A 58-year old woman was admitted to the GI department of the hospital with abdominal colic and fever. Her medical history revealed a cholecystectomy, ERCP with papillotomy, ovariectomy and recently Aspergillosis of the sinuses. She was not known with immune disorders or pulmonary Aspergillosis. She reported to be allergic to a number of drugs (i.e. vancomycin, ciprofloxacin, lidocain and possibly penicillin). This had never been confirmed by skin tests. She was not using any medications on admission.

For a presumptive diagnosis of choledocholithiasis with cholangitis an ERCP was performed. This procedure was complicated by a perforation of the common bile duct and the development of a retroperitoneal abscess. The abscess was drained, and she was consecutively treated with a number of antibiotics: cefuroxime, metronidazole, ciprofloxacin, piperacillin/tazobactam, amoxicillin and vancomycin. On the 56th day after admission she developed a rash and fever while she was being given vancomycin and ciprofloxacin. She was thought to have an allergic reaction to vancomycin and/or ciprofloxacin and the antibiotics were discontinued. E. Coli en Enterococcus Faecium were cultured from the abscess. Prednisone, clemastine, linezolid and cotrimoxazole were started. On the 65th day after admission she developed high fever and a generalized rash (figure 1) accompanied by hypotension, oliguria, and hypoxic respiratory failure. The laboratory results showed a hemoglobin of 5.7 mmol/L, hematocrit 0.28 L/L, white-cell count 13.5 10^9/L, differentiation: eosinophils 3.59 10^9/L, basophils 0 10^9/L, metamyolcytes 0.22 10^9/L, neutrophils 13.01 10^9/L, lymphocytes 1.79 10^9/L, monocytes 0.22 10^9/L, normoblasts +. Platelets 194 x 10^9/L, BUN 10.8 mmol/L, creatinine 178 µmol/L, bilirubin 6 µmol/L, γ-GT 41 U/L, ASAT 51 U/L, Alkaline Phosphatase and ALAT were not elevated. Lactate of 4.7 mmol/l, C reactive protein of 69 mg/ml. Blood gas analysis showed a respiratory compensated metabolic acidosis and a severe hypoxia (pH 7.34, pCO2 33 mmHg [4.4 kPa], pO2 28 mmHg [3.7 kPa], HCO3 17.7 mmol/l, BE -6.9 mmol/l, O_2sat 44.6%). Blood cultures and cultures taken from drain fluid were negative. Tests for cellular immune response showed an absolute decrease of CD8 T-cells (0.13 x 10^9 [normal values 0.3-0.8]) with 1.183 x 10^9 CD4 cells and CD4/CD8 ratio 9.1 [normal values 1.0-3.6]). Chest/abdominal CT showed no focus of infection but signs of ARDS. She was transferred to the Intensive Care Unit where she was intubated. With the presumptive diagnosis of septic shock due to pneumonia, she was treated with cefuroxime, hydrocortisone, fluid resuscitation, and vasopressors. Because of renal failure, renal replacement therapy was started with continuous venovenous hemofiltration with unfractionated heparin as anticoagulant. Empiric antimycotic therapy with caspofungin was started to treat a presumptive invasive Aspergillosis. Meanwhile, the serum lactate and leucocytosis remained high and eosinophilia developed, which kept rising during the following days (see figure 3). Within five

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days after ICU admission the patient developed a maculopapular inflammatory rash starting on the trunk and spreading out to the extremities together with facial redness. Within days the lesions were confluating to erythroderma with sporadic vesicles and blisters with transient fluid mostly on the lower arms, wrists, and sporadically on the trunk. The hands were swollen with a livid-red discoloration. The redness on the lower legs was less intensive and showed a reticulate pattern like livedo reticularis as can be seen in small vessel vasculitis or as a sign of hypoperfusion.

Two days after ICU admission all antibiotics and antimycotics had been discontinued because DRESS syndrome was suspected as all bacterial and fungal cultures had remained negative. A skin biopsy of the rash revealed a mild, chronic dermatitis with eosinophilia (figure 2). No signs of vasculitis were seen. However, no skin biopsy was taken from skin affected by livedo reticularis. Serum ANA and ANCA were negative as was serum Galactomannan antigen. No tests were performed for viral hepatitis, EBV, CMV, HHV-6 infection or Chlamydia/Mycoplasma infection which have been described to be associated with DRESS. No bone marrow biopsy was performed to rule out a hypereosinophilic syndrome or a myeloproliferative disorder. She was not treated with intravenous immune globulin. On the 10th day after ICU admission she became unresponsive. Cortical and brainstem functions were absent and a large intracerebral haemorrhage was found on the CT scan. Lab results showed a prolonged coagulation time (APTT 58 seconds, PTT 28 seconds) associated with the use of heparin. She died after supportive care was discontinued. A post-mortem was not permitted by the family.

Discussion

A life-threatening severe adverse drug reaction characterized by skin rash, fever, lymph node enlargement and single or multiple organ involvement is called drug rash eosinophilia and systemic symptoms (DRESS). DRESS is a rare syndrome which may be life-threatening [4-6]. Systemic symptoms can present with skin rashes, fever, leucocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunction [2-6]. In the literature, diagnostic criteria are described for this condition [5] (table 1). Hematologic abnormalities are a common feature, especially eosinophilia and mononucleosis-like atypical lymphocytosis [2-4]. The skin rash is characterized mostly by a generalized maculopapular erythematous rash which may extend to exfoliative dermatitis or erytrodermia. Less frequently blistering is reported. The severity of cutaneous changes does not necessarily reflect the severity of internal organ involvement [6].

The syndrome has a delayed onset of symptoms in relation to the introduction of the offending drug and worsening of the clinical symptoms after discontinuation of the responsible drug [7]. The syndrome typically starts within 8 weeks after initiation of the involved drug [2-4]. A number of drugs are associated with DRESS [2,4-6]. Drugs most commonly associated with DRESS are anticonvulsants, antidepressants, sulfonamides, Non-Steroidal Anti-Inflammatory Drugs, antibiotics, ACE-inhibitors and beta blockers.

A few laboratory tests can help differentiate DRESS syndrome from other severe drug reactions or severe sepsis. These tests include complete blood cell count, total eosinophils and leucocyte differentiation. Skin biopsy may help differentiating, but is usually not specific [2]. Histology may show a lymphocytic infiltrate, sometimes mimicking cutaneous lymphoma [7]. In this case skin biopsy was inconclusive. Confirming drug-induced allergic reactions by testing the drug is very difficult.

Epicutaneous tests are available but seldom positive. Intracutaneous tests with different concentrations of the causative drug are needed, but it can be a risk for the patient and those tests are mostly false positive [6,7]. Patch testing might be

Figure 1. Maculopapular erythematous generalized rash.

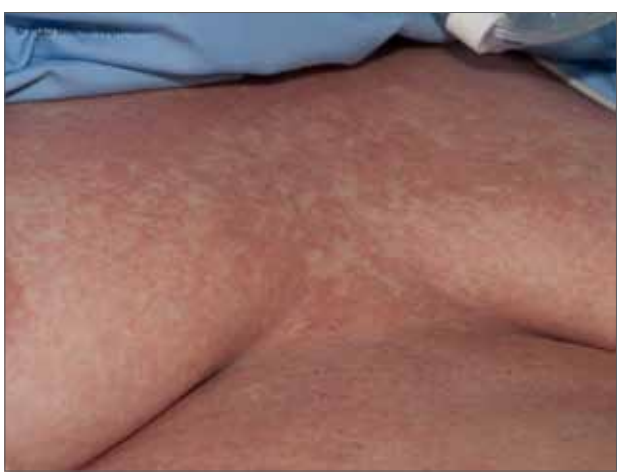
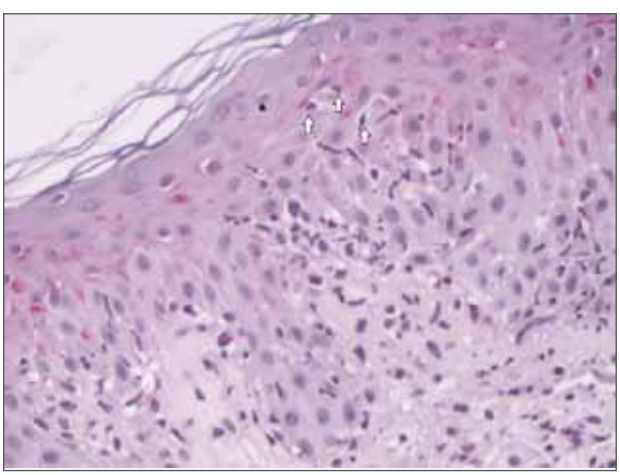


Figure 2. Skin biopsy showing lymphocytic infiltration of the epidermis with only sporadic eosinofilic granulocytes.



The asterix shows the epidermis and the arrows show lymphocytic infiltration of the epidermis.

useful in diagnosing anticonvulsant hypersensitivity syndrome; the usefulness of this test has yet to be determined. Moreover, during the acute phase of the reaction the patch test is not reliable. The advice is to apply patch testing 2 to 6 months after the reaction [9].

The differential diagnosis of DRESS syndrome includes Stevens-Johnson syndrome, toxic epidermal necrolysis, toxic shock syndrome, staphylococcal scalded skin syndrome, hypereosinophilic syndrome, Kawasaki disease, (adult) Still's disease and sepsis. The pathogenic mechanisms are not fully understood but are suggested to be multifactorial [2-4]. Most adverse effects of drugs, are due to the pharmacologic action of a drug, or are idiosyncratic and immune-mediated side effects, which are not predictable. Delayed hypersensitivity reactions are type IV reactions, mediated by T cells. Various T-cell–mediated immune mechanisms lead to clinically distinct diseases. MHC molecules present peptides of different origin (amongst them of drugs) and stimulate different T-cells. Stimulation of $CD8^+$ T-cells and $CD4^+$ T-cells causes secretion of cytokines and activation of other immune effector cells (among which eosinophils and monocytes), which may cause systemic reactions. A drug might not be chemically reactive itself, but become reactive during metabolism and result in an immune reaction. A third possibility is chemically inert drugs, unable to covalently bind to peptides or proteins, that may still activate certain T cells that happen to bear T-cell receptors that can interact with the drug [8]. Shiohara et al. [7] reported a coincidence between patients with DRESS syndrome and HHV-6 reactivation. The human herpesvirus remains latent in lymphocytes after the primary infection and may be reactivated in various conditions such as immunosuppression. HHV-6 DNA was detected in skin lesions of patients with drug hypersensitivity syndrome, but was negative in peripheral blood mononuclear cells.

The therapy of DRESS syndrome includes withdrawal of the offending drug. Supportive therapy includes antipyretics, systemic corticosteroids for reducing symptoms of delayed hypersensitivity reactions. N-acetylcysteine may inhibit the immune reactions involved in the pathogenesis of DRESS reactions and is a precursor of glutathione, which is involved in the detoxification pathway of several drugs [2-4]. Intravenous immune globulin should also be considered in the treatment of severe DRESS syndrome, but evidence for benefit from this treatment is lacking [4]. Family members of the patients should be informed of the diagnosis DRESS as it is inheritable.

In the case presented here, DRESS syndrome was the probable diagnosis by the combination of fever, eosinophilia, skin

Table 1. Diagnostic score for validation of DRESS/Hypersensitivity Syndrome (Kardaun et al. 2007)

ASSESSMENT/SCORE	-1	0	1	2	MIN	MAX
Fever ≥ 38.5	n	y			-1	0
Enlarged lymph nodes		n/u	y		0	1
Eosinophilia Eosinophilia Eosinophilia, if leucocyte count < 4000		n/u	700-1499/µl 10-19.9%	≥ 1500/µl ≥ 20%	0	2
Atypical lymphocytes		n/u	y		0	1
Skin involvement Skin rash extent (%BSA) Skin rash suggesting DRESS Histology suggesting DRESS	 n n	 n/u u y/u	 >50% y		-2	2
Organ involvement* Liver Kidney Lung Muscle/heart Pancreas Other organ		 n/u	 y y y y y y		0	2
Resolution ≥ 15 days	n	y			-1	0
Serology/PCR Hepatitis A, B, C EBV; CMV Mycoplasma/Chlamydia ANA Blood culture If none are positive and at least 3 negative			 y		0	1
Total					-4	9

y = yes, n = no, u = unknown

* After exclusion of other causes: 0 = no organ involvement, 1 = 1 organ, 2 = ≥ 2 organs

Final score: < 2: excluded, 2-3: possible, 4-5: probable, >5: definitive

involvement, and negative blood cultures (a score of five criteria according to the diagnostic score for validation of DRESS). The patient was treated by discontinuation of all possible disease associated medications and supportive treatment was started with corticosteroids, mechanical ventilation, and continuous renal replacement therapy. She did not receive treatment with immune globulins and no tests were performed for viral pathogens.

Tests for cellular immune response showed an absolute decrease of CD8 T-cells with normal CD4 cell count eliminating the possibility of immunodeficiency. Changes in CD4 and CD8 cell count have been described in patients with sepsis [10] and are associated with both the systemic inflammatory response syndrome and the compensatory anti-inflammatory response syndrome.

Intracerebral haemorrhage has not been previously described in DRESS syndrome, and seems to be unrelated.

Conclusion

A case of multiorgan dysfunction syndrome and rash is described here with an allergy for a drug without evidence for sepsis. DRESS is a rare syndrome which may be life-threatening. Early recognition of this syndrome is difficult but vital to enable initiation of treatment at an early stage. The most important features of this condition are rash, eosinophilia and high fever. Treatment consists of withdrawal of the offending drug, supportive therapy, antipyretics and systemic corticosteroids.

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CASE REPORT

Fatal Neuroleptic Malignant-like Syndrome in a Patient with Severe Parkinson's Disease

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Abstract - ***Introduction*** The neuroleptic malignant syndrome and the serotonin syndrome are related and potentially fatal disorders. Their presentation can be similar and treatment is mainly supportive. ***Case*** A 63-year-old woman with a history of severe Parkinson's disease presented with an altered mental status, autonomic instability, severe hyperthermia and respiratory failure. There were no signs of infection and she developed a renal function impairment. Her comatose state was persistent and a magnetic resonance imaging scan finally showed bilateral thermal injury in the basal ganglia and cerebellum. She died twelve days after admission. ***Discussion*** The neuroleptic malignant syndrome and the serotonin syndrome can be hard to distinguish at clinical presentation. The neuroleptic malignant syndrome is mostly caused by the initiation of antidopaminergic agents but can also be due to an acute shortage of dopaminergic activity as seen in severe Parkinson patients. In these patients this syndrome is often caused by withdrawal of dopaminergic therapy but other triggers have also been described. The time of onset and a careful evaluation of the patient's medical and drug histories are the key to diagnosis and differentiation from related disorders. Causative agents should be abandoned in both syndromes and dopaminergic agonists should be initiated for the neuroleptic malignant syndrome. ***Conclusion*** Early recognition is important for the management of the neuroleptic malignant syndrome and the serotonin syndrome. In severe Parkinson patients a variant of the neuroleptic malignant syndrome known as the neuroleptic malignant-like syndrome or the parkinsonism hyperpyrexia syndrome may exist.

Keywords - **Neuroleptic Malignant Syndrome; Serotonin Syndrome; Parkinson Disease; Hyperthermia; Intensive Care; Magnetic Resonance Imaging**

Introduction

The Neuroleptic Malignant Syndrome (NMS) and the Serotonin Syndrome (SS) are related and potentially fatal entities. Both can present with severe hyperthermia, an altered mental status and autonomic instability. General treatment for both syndromes consists of supportive care and removal of the causative agent. Complications include aspiration pneumonia, respiratory failure, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation (DIC) and thromboembolic events. [1-3]

A variation of the NMS is seen in patients with severe Parkinson's disease (PD). In the literature, different names for the condition such as the neuroleptic malignant-like syndrome (NMLS), the Parkinsonism Hyperpyrexia Syndrome (PHS) and the dopaminergic malignant syndrome are used. It is mostly seen after sudden withdrawal of levodopa therapy, but other known triggers include infection, dehydration, poor oral intake and excessively hot weather. [4]

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Case

A 63-year old woman with a history of severe PD was referred to the emergency department. In the few days prior to admission she had complained of agitation, restless movements, fever and dysphagia. Her drug therapy consisted of levodopa 250 milligrams (mg) 7 times daily, pramipexole 4.5 mg once daily, amantadine 100 mg twice daily, rivastigmine 9.5 mg once daily, selegiline 5 mg twice daily and tolcapone 100 mg three times daily. No recent changes had been made to this medication.

Table 1. Differences in Manifestation of the Neuroleptic Malignant Syndrome and the Serotonin Syndrome.

	NEUROLEPTIC MALIGNANT SYNDROME	SEROTONIN SYNDROME
Onset	Several days	Within 12-24 hours
Causative agents	Dopamine antagonist	Serotonin agonist
	Withdrawal of levodopa therapy	
Neuromuscular	Bradyreflexia	Hyperreflexia
Rigidity	Increased tone	
Resolution	Days to weeks	Within 24 hours

At presentation she was comatose (E1M4V1). Because of respiratory failure and hemodynamic instability she was intubated and mechanical ventilation and inotropic support were initiated in the intensive care unit (ICU). Her central body temperature rose as high as 43 degrees Celsius and active cooling measurements like ice packs, cold infusion and cold air were started. Peripheral motor reflexes were absent. There was no evident muscle rigidity. An abdominal, thoracic and cerebral computed tomography (CT) scan were performed and did not show any abnormalities. Infection parameters were negative and further laboratory evaluation showed a thrombopenia (10 .10^9 U/l) and an elevated creatine kinase (1200 U/l). Dantrolene therapy was considered but was not started because of the absence of muscular rigidity. The next day an electro-encephalogram (EEG) ruled out a non-convulsive status epilepticus. She was still comatose while no sedation was being used. Lumbar puncture was performed and cerebrospinal fluid tests were normal. Her infection parameters and all cultures stayed negative during the whole admission period. Despite cold air and cold infusion therapy her body temperature remained between 38 and 39.5 degrees Celsius. She developed a moderate renal function impairment (creatinine 300 µmol/l on day 4) which later showed spontaneous recovery. A clear diagnosis was still lacking and due to concerns for an SS or an NMS, all medication with possible serotonergic activity (selegiline) or antidopaminergic activity (amantadine and tolcapone) was stopped. Her other regular therapy was continued.

Because of her prolonged comatose state (E1M1V1) a second cerebral CT scan was performed three days after admission. This time bilateral hypodense areas were seen in the basal ganglia. A second EEG again ruled out a status epilepticus on day 6 and there were signs of a generalized encephalopathy. A magnetic resonance imaging (MRI) scan was performed on day 7 which showed symmetrical injury in the basal ganglia and cerebellum on both sides. (Figures 1 and 2) No sedative agent had been given since the second day of admission.

Based on her further persistent coma and the finding of a worsening severe encephalopathy on a third EEG performed on day 11, the decision to withdraw supportive care was made. The patient died after 12 days of ICU stay.

Discussion

The NMS and the SS are hard to distinguish at clinical presentation. The main clinical features like hyperthermia, an altered level of consciousness and autonomic instability are similar. Other findings such as muscle rigidity, rhabdomyolysis, respiratory failure, renal failure and DIC can be present in both conditions. Laboratory findings can include leucocytosis, metabolic acidosis, elevated creatine kinase, and liver or renal function impairment [1-3]. As well as the similarities described above, there are some important differences in the manifestation of these conditions. The time of onset and the patient's medical and drug history play a major role in a clinical differentiation being made, while other possible causes should be excluded (Tables 1 and 2).

The precise pathophysiological mechanisms in the NMS and the SS are unknown. While the primary mechanism in the NMS should be a sudden suppression of central dopamine pathways caused by antidopaminergic agents, the primary mechanism in the SS is an alteration in central serotonin metabolism due to serotonergic agents. Further pathologic mechanisms involved are sympathicoadrenal dysfunction and abnormal calcium availability in skeletal muscle cells. [1-3]

The first step in management for both the NMS and SS consists of abandoning the causative agent, concerning antidopaminergic agents in the NMS and serotonergic agents in the SS. Supportive care as ICU monitoring, intravenous fluid replacement, active cooling and hemodynamic and respiratory support should then be started. Sedation, mechanical ventilation, antibiotics and hemodialysis may be necessary. Dopaminergic therapy

Figure 1. Axial DWI; areas of restricted diffusion in the basal ganglia.

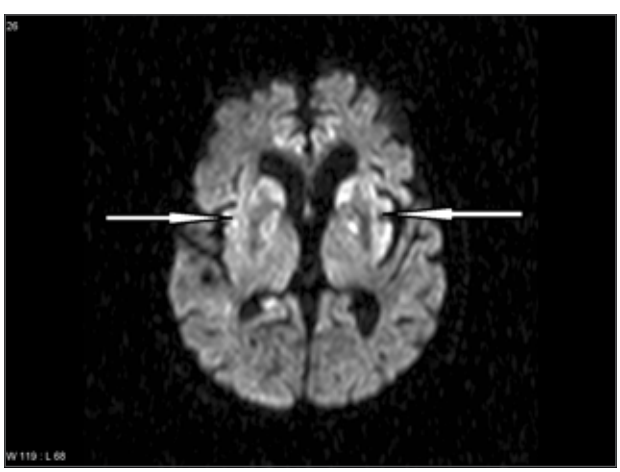
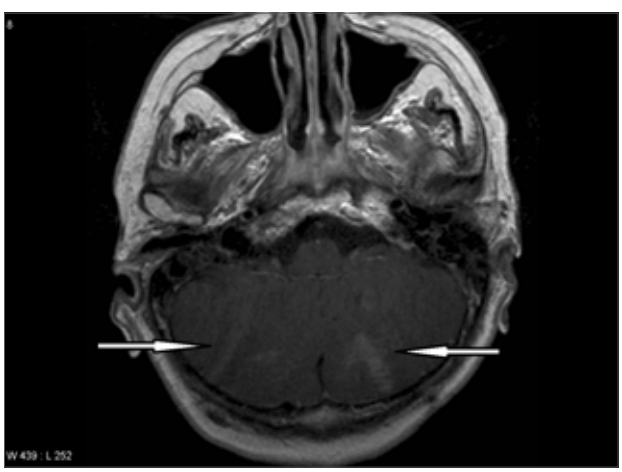


Figure 2. Axial postgadolinium T1-weighted image; bilateral cerebellar patchy enhancement.



with levodopa, bromocriptine, pramipexole or apomorphine is recommended for the NMS or the NMLS. Dantrolene is reserved for cases with severe muscle rigidity and rhabdomyolysis. [1-4]

The patient in our case probably suffered from a variant of the NMS – known as the NMLS or the PHS. This syndrome is seen in severe Parkinson patients without a necessary change in dopamine agonist therapy. Other triggers like infection, dehydration, hot weather or starvation, are thought to cause a sudden suppression in central dopaminergic activity. [4]

Severe hyperthermia, an altered mental status, autonomic instability, respiratory failure, renal function impairment and signs of rhabdomyolysis (elevated creatinine kinase) and DIC (thrombopenia) were all present in this case. Selective injury in the basal ganglia and cerebellum on an MRI scan as presented in our case has been described before and is thought to be direct thermal damage. Neuropathological studies show Purkinje cell necrosis and gliosis in these areas. The cerebellum especially is vulnerable to thermal damage although the exact mechanism of this is not fully understood. [5]

A diagnosis was made relatively late in our case and no clear differentiation was made between the NMS and the SS. All medication with possible serotonergic or antidopaminergic activity rarely reported was stopped. A better understanding of these disorders and the awareness of an entity like the NMLS in Parkinson patients would have made recognition more easy. Instead of stopping some of the patient's regular medication, it probably would have been more appropriate to start additive dopaminergic therapy in this perspective.

Conclusion

Early recognition is important for the treatment of the NMS and the SS as the causative agent should be abandoned and dopaminergic agonists should be initiated for the NMS. The time of onset and the patient's medical and drug history are the key to diagnosis, while other possible causes should be excluded. In severe Parkinson patients there is a variant of the NMS known as the NMLS or PHD that may exist. It is seen without a necessary change in dopamine agonist therapy.

Table 2. Differential diagnosis of the Neuroleptic Malignant Syndrome.

Infectious	Meningitis, Encephalitis, Brain abscess, Sepsis
Pharmacologic	Serotonin Syndrome, Anticholinergic Syndrome, Malignant Hyperthermia, Withdrawal of Dopaminergic Agents or Baclofen
Endocrine	Thyrotoxicosis, Pheochromocytoma

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