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A Rare Complication of Seasonal Influenza: Case Report and a Brief Review of the Literature

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Abstract Acute viral myositis is a rare condition that is commonly defined with influenza A, B, and enterovirus in the United States of America. Viral myositis complicated by rhabdomyolysis is even less common but requires prompt attention and diagnosis to prevent complications. We describe the occurrence of acute viral myositis complicated by rhabdomyolysis in a young 43-year-old man that lead to acute renal failure. It also highlights that clinicians should keep in mind that viral upper respiratory infections can be complicated with various clinical manifestations that could extend beyond respiratory symptoms.

Keywords: *influenza, rhabdomyolysis, acute kidney injury, myositis, viral myositis*

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1. Introduction

Acute viral myositis is a rare defined complication of influenza [1,2,3]. Viral myositis occurs in the early recovery phase of influenza [4]. Cases have been defined with both influenza A and B [1-10]. In most cases, patients present with an isolated elevation of serum creatine kinase levels. Most of the cases are in the pediatric population, however viral myositis is universally found in the adult population as well [1,3]. During the influenza pandemic of 2009, there are many reported cases in adults as well [5,6,7] Some rare cases of rhabdomyolysis and severe myositis associated with influenza infections are also defined in the literature [6-12]. Cases of rhabdomyolysis are more commonly associated with influenza A [1,5,6,7,8,9]. The pathophysiology leading to myositis is unclear and several hypotheses have been postulated. Several studies listed the three possible mechanisms responsible for triggering muscle breakdown and in severe cases leading to rhabdomyolysis which include direct muscle invasion by the influenza virus, viral toxins causing direct muscle damage and cytokine storm triggered by the immunologic reaction [11,13,14]. Viral studies have also shown the NB protein found in influenzas B may have myotropic properties and can serve as an entity for viral entry [15]. Here, we present an interesting case of rhabdomyolysis and acute renal failure in a 43-year-old man who was diagnosed with influenza B.

2. Case Presentation

A 43-year-old man with no significant past medical history presented to our Institution with a four-day history of fevers, myalgias, cough, arthralgias, and generalized weakness. On the initial presentation, the patient was febrile to 102° F with an oxygen saturation of 88%. His labs were significant for normal leukocyte count with a left shift, elevated creatinine, transaminitis, and hypocalcemia. The lactate was 2.4 mmol/L. His procalcitonin was inconclusive at 0.55 ng/ml. Initial creatinine kinase (CK) was 1289 ng/ml. Blood cultures were drawn. The initial chest X-ray showed minimal left lower lobe atelectasis. A chest CT scan showed left lower lobe consolidation with a focus of right lower lobe consolidation as well. The patient was started on intravenous fluids as well as ceftriaxone and azithromycin due to underlying concern for pneumonia. The patient was then admitted for further work-up. The respiratory viral panel was positive for influenza B. Urinalysis was positive for red blood cells and proteinuria. Blood cultures and sputum cultures were negative. Urine legionella and urine streptococcal antigens were negative as well. The patient was continued on IV antibiotics however, his hospital course got complicated by up trending creatinine and CK, worsening edema, decreased urine output with a change in urine color to dark brown. Some further testing was done including urine myoglobin and urine osmolality which were abnormal. In the setting of worsening acute renal injury, proteinuria and hematuria implying a glomerular cause of AKI, nephrology and rheumatology services were consulted. Renal biopsy was done to delineate the underlying pathophysiology. Thyroid function tests were within normal limits. As per rheumatology recommendations, an extensive workup for autoimmune causes was done. The patient was tested for ANA, Anti ds-DNA, LKM Ab, complement levels, anti-smooth muscle cells Ab, p-ANCA, c-ANCA, Anti Jo-1 antibodies, glomerular basement

membrane antibodies, anti-streptolysin-1 antibodies and myositis panel which came back negative. Extensive lab work up lacked enough evidence to suggest a rheumatological connective tissue disease in this previously young healthy male with negative serologies and acute presentation. Clinical history of acute onset of symptoms is also not typical of an inflammatory autoimmune myopathy, furthermore it is also atypical for an inflammatory myopathy to present with glomerular disease.

Patient's kidney function deteriorated and required the need for urgent hemodialysis in the setting of hypocalcemia and fluid overload. His CK levels were trended daily. A week after starting hemodialysis, CK levels and creatinine levels started to downtrend. The urine output improved, and peripheral edema decreased. Two weeks after initiating hemodialysis, the dialysis catheter was removed. During a follow-up visit two weeks after discharge, the kidney function continued to show improvement with creatinine level dropping to 1.64mg/dL. The kidney biopsy findings were significant for acute tubular necrosis with tubular casts, a plausible explanation was tubular injury secondary to myoglobin.

Table 1. Complete Blood Count

Laboratory data	**Reference Range**	**Admission**	**1st week**	**2nd week**	**3rd week**
White blood cells (K/ul)	3.80 - 10.50	6.76	11.85	9.47	5.60
Red blood cells (M/ul)	4.20 - 5.80	6.24	4.07	3.81	4.31
Hemoglobin (g/dl)	13.0 - 17.0	17.1	11.3	10.5	11.7
Hematocrit (%)	39.0 - 50.0	50.4	32.8	31.7	36.8
Mean corpuscular volume (fl)	80.0 - 100.0	80.8	83.2	80.6	85.4
Mean corpuscular hemoglobin (pg)	27.0 - 34.0	27.4	27.8	27.6	27.1
MCHC (gm/dl)	32.0 - 36.0	33.9	34.5	33.1	31.8
RDW (%)	10.3 - 14.5	12.4	12.8	13.0	12.7
Platelets (K/ul)	150 - 400	186	367	396	539
Neutrophil (%)	43.0 - 77.0	80.4	78.9	75.6	43.3
Lymphocyte (%)	13.0 - 44.0	9.2	10.5	11.3	42.3
Monocyte (%)	2.0 - 14.0	7.7	8.1	10.1	9.6
Eosinophil (%)	0.0 – 6.0	0.75	1.4	1.8	3.0
Basophil (%)	2.0	0.52	0.3	0.2	1.4
Neutrophil Abs (K/ul)	1.80 – 7.40	7.7	9.35	7.16	2.42
Lymphocyte Abs (K/ul)	1.00-3.30		1.25	1.07	2.37
Monocyte Abs (K/ul)	0.00 – 0.90		0.96	0.96	0.54
Eosinophil Abs (K/ul)	0.00 – 0.50		0.16	0.17	0.17
Basophil Abs (K/ul)	0.00 – 0.20		0.03	0.02	0.08
Immature Gran (%)	0.0 – 1.5				0.4
MPV			9.2	9.3	

MCHC mean corpuscular hemoglobin concentration **RDW** red cell distribution width **Abs** absolute count.

Table 2. Comprehensive metabolic panel

Serum	Reference Range	On Admission	1st week	2nd week	3rd week	2 weeks follow-up
Anion gap (mEq/L)	5 - 15	21	25	17	18	14
Sodium (mmol/L)	136 - 146	133	129	136	140	137
Potassium (mmol/L)	3.5 - 5.0	4.6	5.5	5.4	3.9	4.7
Chloride (mmol/L)	98 - 106	90	75	96	97	101
Bicarbonate (mmol/L)	24 - 31	22	29	23	25	22
Blood Urea Nitrogen (mg/dl)	8.0 - 23.0	42	124.0	81.0	57.0	33
Creatinine (mg/dl)	0.70 – 1.20	3.21	16.86	14.63	5.84	1.64
Glucose (mg/dl)	70 - 99	109	86	79	91	102
ALT (SGPT) U/L	0 - 31	455	343	107		
AST (SGOT) U/L	10 - 35	1882	379	71		
Alk Phos U/L	25 - 125	72	94	95		
Total bilirubin (mg/dl)	0.0 - 1.2	0.7	0.4	0.4		
Calcium (mg/dl)	8.8 - 10.2	7.2	6.6	9.2	8.5	10.1
Total protein (g/dl)	6.4 - 8.3	7.5	5.0	6.1		
Albumin (g/dl)	2.8 - 5.7	4.1	2.5	3.1		
Phosphorous (mg/dl)	2.5 - 4.5		2.50			
Magnesium (mg/dl)	1.60 - 2.60		11.0	7.7		
GFR - AA (ml/min/1.73m2	>=60.0	25.8	3.8	4.5	12.9	58
GFR Non-AA (ml/min/1.73m2)	>=60.0	21.3	3.1	3.7	10.6	50
Creatine Kinase (ng/ml)	20 - 200	1289	>22,000	10,873	382	

*__ALT__ alanine aminotransferase, **AST** aspartate aminotransferase, **Alk Ph** alkaline phosphatase, **AA** African American.

Table 3. Urinalysis

	Day 1	Day 5
Specific gravity	1.018	1.016
Protein	>=300	>=300
Glucose	100	100
Ketones	Negative	Trace
Bilirubin	Negative	Negative
Blood	Large	Large
Urobilinogen	0.2	0.2
Nitrite	Negative	Negative
Leukocyte esterase	Trace	Trace
Squam. epithelial cells	0 - 5	0 - 5
White blood cells	10 - 20	10 - 20
Red blood cells	10 - 50	10 - 20
Bacteria	None Seen	None Seen
Hyaline Cast	0 - 5	None Seen
pH	5.5	7.0
Appearance	Cloudy	Cloudy
Color	Dark Yellow	Dark Yellow

Table 4. Other Labs

Serum	**Reference Range**	**Patient**
Thyroid-stimulating hormone (uIU/ml)	0.270 – 4.200	2.830
Free thyroxine (ng/dl)	0.93 – 1.70	1.17
Triiodothyronine (mg/dl)	80.0 - 200	55
Serum osmolality (mOsm/kg)	275 - 295	292
Serum myoglobin (ng/ml)	16 - 96	49660
ESR (mm/hr)	0 - 15	25
CRP (mg/l)	1.00 – 4.00	134.12
Procalcitonin (ng/ml)	0.00 – 0.50	0.55
Sjogren's antibodies (SS-A, SS-B) (Al)	< +0.9	< 0.2
LKM- antibodies (units)	0 - 20	< 20.1
Anti-smooth muscle Cells Antibodies	< 1: 20	< 1:20
Anti-nuclear Antibodies	< 1: 80	Negative
Anti-streptolysin O Ab (IU/ml)	0 - 199	136
c- ANCA Ab	Negative	Negative
Atypical ANCA Ab	Negative	Negative
p- ANCA Ab	Negative	Negative
Complement 3 (mg/dl)	86 - 184	100
Complement 4 (mg/dl)	20 - 58	38
Anti-Ds DNA Ab (IU/ml)	<=29	<12
Anti-Jo 1 Ab (units)	<20	<20
Anti- GBM Ab (Al)	<1.0	<1.0
Urine Studies		
Urine Osmolality (mOsm/kg)	300 - 1000	246
Urine myoglobin (mcg/L)	<=21	>5000
24-hour urine creatinine (mg/dl)	39 - 259	212.55
Protein/creatinine ratio	22 - 128	889
Urine sodium (mmol/L)	<60	<60
Urine chloride (mmol/L)	<60	<60
Urine potassium (mmol/L)		23.5
MyoMarker™ Panel 3		
Anti Jo-1 Ab (Units)	<20	<20
PL-7	Negative	Negative
PL-12	Negative	Negative

EJ	Negative	Negative
OJ	Negative	Negative
SRP	Negative	Negative
MI-2	Negative	Negative
TIF GAMMA (P155/140) (Units)	<20	<20
MDA-5 (P140) (CADM-140) (Units)	<20	<20
NXP-2 (P140) (units)	<20	<20
Anti-PM/SCI-100 AB (Units)	<20	<20
Fibrillarin (U3 RNP)	Negative	Negative
U2 snRNP	Negative	Negative
Anti-U1-RNP (units)	<20	<20
KU	Negative	Negative
Anti-SS-A 52 KD , IGG (Units)	<20	<20
Immunoglobulin Panel		
Immunoglobulin G	610 – 1660 mg/dl	969
Immunoglobulin A	84 – 499 mg/dl	217
Immunoglobulin M	35 – 242 mg/dl	27
Immunoglobulin Kappa FLC	0.33 – 1.94 mg/dl	11.24
Immunoglobulin Lambda FLC	0.57 -2.63 mg/dl	6.93
Kappa Lambda FLC ratio	0.26 – 1.60	1.62

Ab antibody, **ESR** erythrocyte sedimentation rate, **CRP** C-reactive protein, **ANCA** anti-nuclear cytoplasmic antibodies **FLC** free light chains.

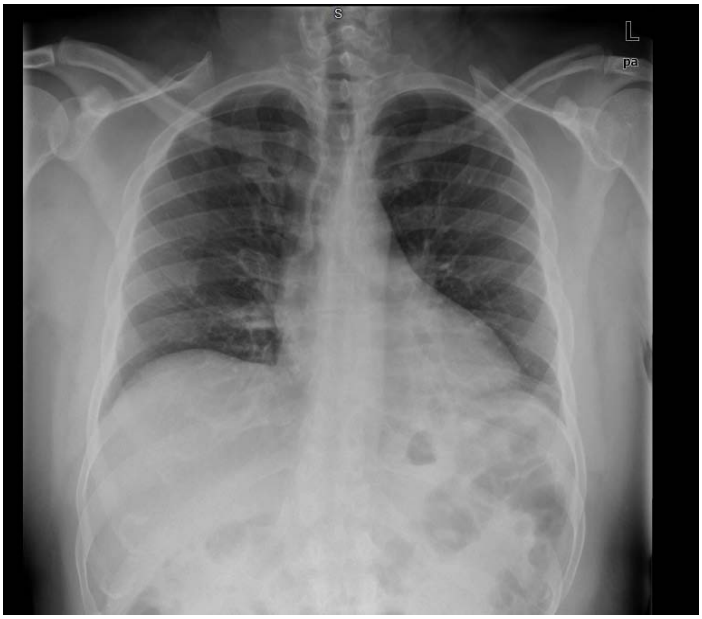

Image 1. Chest radiograph revealing left lower lobe atelectasis

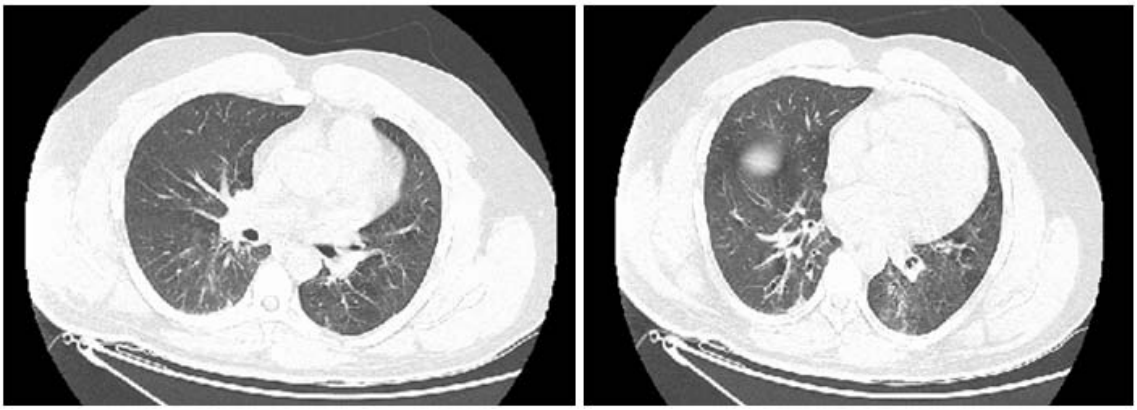

Image 2. Computed tomograhy of the chest without contrast demonstrating lef lower lobe consolidation and foci of right lower lobe consolidation compatible with pneumonia. Scattered mediastinal lymphadenopathy likely reactive are also seen

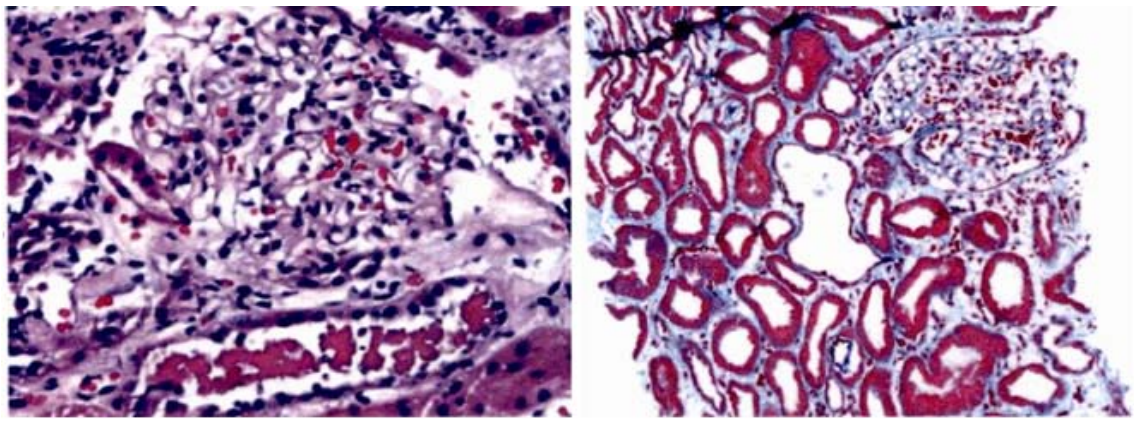

Image 3. A (left, glomerulus and cast) and **3B** (right, glomerulus and acute tubular epithelial cell injury). Renal biopsy showed no hypercellularity, necrosis, and crescents in the glomeruli. Foci of tubular casts with fuchsinophilia, ectatic angulated tubular profiles with foci of tubular epithelial cell simplification, interstitial edema and patchy mononuclear interstitial inflammation with plasma cells are present

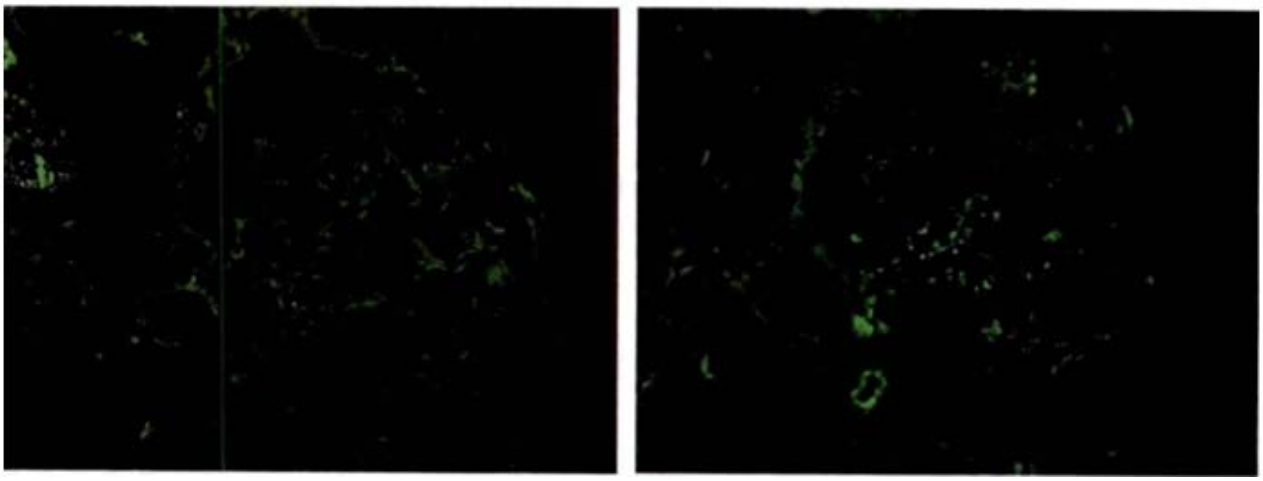

Image 4. Negative Immunofluorescence studies IgA (left), C3 complement (right)

Direct Immunofluorescence The glomeruli have no staining with antisera specific for IgG, IgA, IgM, C1q, kappa light chains, and lambda light chains. The glomeruli have granular mesangial, mostly hilar, staining with anti-serum specific for C3 (1+). Scattered interstitial plasma cell cytoplasmic reactivity with antisera specific for IgG, kappa light chains and lambda light chains are present. Weak tubulointerstitial fibrinogen usual reactivity is present and usual reactivity with antiserum specific for albumin is present

3. Discussion

Acute viral myositis complicated by rhabdomyolysis is rare but can be a very serious and life-threatening complication of influenza infection which presents itself as a global burden every year [1-11]. It has been defined with the following virus: influenza [1-12,15], coxsackievirus [13], Epstein-Barr virus[16], adenovirus[17], echovirus [18], cytomegalovirus[19], measles virus [20], varicella-zoster virus [21], human immunodeficiency virus [22], dengue virus [23], parainfluenza [24], and herpes simplex virus [25]. According to one study, the most common viral agent responsible for viral-induced rhabdomyolysis is the influenza virus reported in 33% of cases [26]. In another retrospective study of the pediatric population, 38% of cases of rhabdomyolysis were viral induced [27].

Some studies highlighted that elevated CK levels are associated with worse complications as a result of influenza infection and this trend was noted in the 2009 pandemic of influenzas infection [28,29]. For diagnosis of rhabdomyolysis, a preceding viral infection is a clue with elevated CK levels. With underlying rhabdomyolysis, it is not uncommon to get very high levels of CK levels >100,000 U/L. Also, transaminitis, elevated creatinine, and myoglobinuria are present as a sequel. It is more likely to detect an underlying virus responsible early in the course of infection. In the detection of viral myositis, a muscle biopsy is not a helpful tool as it can be normal or inconclusive [13,26].

The mechanism responsible for causing viral myositis is not clear, there is some hypothesis that suggests the following likely underlying mechanisms:

1. The virus causing direct myocyte invasion. Interestingly, many muscle biopsies done for diagnostic purposes are either normal or inconclusive and, in most cases, a virus has not been detected. One study demonstrated the expression of alpha 2,3 and alpha 2,6- linked sialic acid receptors on muscle cells, which are the same as located on respiratory epithelial cells [10,30].

2. Toxic cytokines that are released by the human body as a result of infection, one study of viral-induced rhabdomyolysis reported elevated levels of tumor necrosis factor in the serum. TNF has shown to cause muscle breakdown in some experimental studies done on animals [10,13].

3. Immunological reaction due to viral infection causing myocyte breakdown. Studies have proposed antigenic mimicry, the release of sequestered antigen or T cells with dual T cells receptors arising in response to infection as underlying possible immunologic reactions [10,14].

Viral myositis is one of the less common complications of influenza infection seen especially in children however, it has been increasingly reported among adults as well. Clinicians should keep in consideration the possibility of rhabdomyolysis in a patient with influenza presenting with generalized body aches, myalgias, and dark urine. Healthcare providers play a significant role in creating awareness about the importance of influenza vaccination. On large study from Japan during the influenza season, 2013-2014 involving more than 300,000 subjects between the ages of 1-64 years demonstrated significant prevention of influenza onset and more effectiveness in reducing the secondary risk of influenza complications [31]. Another study from the 2015-2016 influenza predominant season in the United States demonstrated the protective effects of influenza vaccination for all age groups. It reduced influenza-related hospitalization by 51% in patients who are at risk of developing a serious infection or complications due to underlying comorbidities [32]. Keeping in view that influenza poses a global burden every year, awareness and patient education should be encouraged among our patient population to increase the number of vaccinated individuals in order to prevent both the risk of serious infections and its complications.

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References

[1] Gibson, S.B., et al., Three cases of acute myositis in adults following influenza-like illness during the H1N1 pandemic. J Neurosci Rural Pract, 2013. 4(1): p. 51-4.
[2] Crum-Cianflone, N.F., Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev, 2008. 21(3): p. 473-94.
[3] Lundberg, A., Myalgia cruris epidemica. Acta Paediatr, 1957. 46(1): p. 18-31.
[4] Middleton, P.J., R.M. Alexander, and M.T. Szymanski, Severe myositis during recovery from influenza. Lancet, 1970. 2(7672): p. 533-5.
[5] Patel, M., et al., Pandemic (H1N1) 2009 influenza. Br J Anaesth, 2010. 104(2): p. 128-42.
[6] Ayala, E., et al., Rhabdomyolysis associated with 2009 influenza A(H1N1). JAMA, 2009. 302(17): p. 1863-4.
[7] Lai, C.C., C.Y. Wang, and H.I. Lin, Rhabdomyolysis and acute kidney injury associated with 2009 pandemic influenza A(H1N1). Am J Kidney Dis, 2010. 55(3): p. 615.
[8] Shenouda, A. and F.E. Hatch, Influenza A viral infection associated with acute renal failure. Am J Med, 1976. 61(5): p. 697-702.
[9] Carrillo-Esper, R., et al., [Rhabdomyolysis and acute renal failure in human influenza A H1N1 mediated infection]. Gac Med Mex, 2009. 145(6): p. 519-21.
[10] Agrawal, A., et al., Isolated left upper extremity myositis and severe rhabdomyolysis in an adult with H1N1 Influenza, a case report with literature review. IDCases, 2014. 1(3): p. 43-4.
[11] Fadila, M.F. and K.J. Wool, Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. N Am J Med Sci, 2015. 7(3): p. 122-4.
[12] Ozawa, H., S. Noma, and I. Nonaka, [Myositis and rhabdomyolysis with influenza infection]. Nihon Rinsho, 2000. 58(11): p. 2276-81.
[13] Fodili, F. and E.F. van Bommel, Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection. Neth J Med, 2003. 61(5): p. 177-9.
[14] Craighead, J.E., S.A. Huber, and S. Sriram, Animal models of picornavirus-induced autoimmune disease: their possible relevance to human disease. Lab Invest, 1990. 63(4): p. 432-46.
[15] Betakova, T., M.V. Nermut, and A.J. Hay, The NB protein is an integral component of the membrane of influenza B virus. J Gen Virol, 1996. 77 (Pt 11): p. 2689-94.
[16] Friedman, B.I. and R. Libby, Epstein-Barr virus infection associated with rhabdomyolysis and acute renal failure. Clin Pediatr (Phila), 1986. 25(4): p. 228-9.
[17] Wright, J., G. Couchonnal, and G.R. Hodges, Adenovirus type 21 infection. Occurrence with pneumonia, rhabdomyolysis, and myoglobinuria in an adult. JAMA, 1979. 241(22): p. 2420-1.
[18] Josselson, J., T. Pula, and J.H. Sadler, Acute rhabdomyolysis associated with an echovirus 9 infection. Arch Intern Med, 1980. 140(12): p. 1671-2.
[19] Hughes, G.S., Jr. and R. Hunt, Cytomegalovirus infection with rhabdomyolysis and myoglobinuria. Ann Intern Med, 1984. 101(2): p. 276-7.
[20] Seibold, S., et al., Rhabdomyolysis and acute renal failure in an adult with measles virus infection. Nephrol Dial Transplant, 1998. 13(7): p. 1829-31.
[21] Hollenstein, U., F. Thalhammer, and H. Burgmann, Disseminated intravascular coagulation (DIC) and rhabdomyolysis in fulminant varicella infection--case report and review of the literature. Infection, 1998. 26(5): p. 306-8.
[22] Mahe, A., et al., Acute rhabdomyolysis coincident with primary HIV-1 infection. Lancet, 1989. 2(8677): p. 1454-5.
[23] Acharya, S., et al., Acute dengue myositis with rhabdomyolysis and acute renal failure. Ann Indian Acad Neurol, 2010. 13(3): p. 221-2.
[24] O'Connor, J.V. and S.K. Iyer, Myoglobinuria associated with parainfluenza type 2 infection. N Y State J Med, 1982. 82(10): p. 1469-70.
[25] Schlesinger, J.J., D. Gandara, and K.G. Bensch, Myoglobinuria associated with herpes-group viral infections. Arch Intern Med, 1978. 138(3): p. 422-4.
[26] Tanaka Motoharu, T.M., et al., Acute renal failure due to rhabdomyolysis associated with echovirus 9 infection: a case report and review of literature. Japanese Journal of Medicine, 1989. 28(2): p. 237-242.
[27] Mannix, R., et al., Acute pediatric rhabdomyolysis: causes and rates of renal failure. Pediatrics, 2006. 118(5): p. 2119-25.
[28] Perez-Padilla, R., et al., Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med, 2009. 361(7): p. 680-9.
[29] Borgatta, B., et al, Elevation of creatine kinase is associated with worse outcomes in 2009 pH1N1 influenza A infection. Intensive care medicine 2012. 38(7): p. 1152-1161.
[30] Sullivan, S.J., et al., 2009 H1N1 influenza. Mayo Clin Proc, 2010. 85(1): p. 64-76.
[31] Shibata, N., et al., Correction to: Influenza vaccination effectiveness for people aged under 65 years in Japan, 2013/ 2014 season: application of a doubly robust method to a large-scale, real-world dataset. BMC Infect Dis, 2019. 19(1): p. 709.
[32] Ferdinands, J.M., et al., Prevention of Influenza Hospitalization Among Adults in the United States, 2015-2016: Results From the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN). J Infect Dis, 2019. 220(8): p. 1265-1275.