ORIGINAL RESEARCH PAPER

Pulmonary Medicine

ATYPICAL PNEUMONIA: IS VIRAL PNEUMONIA 'RARE' OR 'RARELY DIAGNOSED'? – CASE REPORT AND REVIEW OF LITERATURE

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Chopra M Md Pulmonary Medicine, Dept Of Pulmonary Medicine, Army Hospital (Research & Referral), Delhi

Agarwal M* Md Pathology And Cytogenetics, Department Of Lab Sciences And Molecular Medicine, Army Hospital (research & Referral), New Delhi,110010 *corresponding Author

ABSTRACT

A young healthy male, with no known comorbidities, presented with progressive fulminant pneumonia. The patient succumbed to death without a conclusive antemortem diagnosis despite extensive investigations. The post mortem revealed features of viral cytopathic changes with extensive hyaline membrane formation in lungs. However, molecular tests performed to establish definitive diagnosis, yielded negative results for all the organisms tested. The aim is to present a case of Viral pneumonia – a diagnosis rarely talked about in scenario of developing countries.

Clinical protocol

A 38 years old male, chronic smoker with smoking index (SI) of 225, became symptomatic, 10 days after returning from a short vacation in Andaman & Nicobar Islands, with acute onset high grade fever associated with chills and rigors. He developed dry cough and breathlessness over next two days. His children, aged 13 years (boy) and 8 years (girl), also developed similar symptoms within 3-7 days of return. Initially, patient took 'over the counter medications' without relief and was admitted on third day of illness at a tertiary care hospital in Udhampur (J&K), for worsening cough, breathlessness, fever and diarrhea.

Clinical examination and investigations

On admission, he was febrile with tachycardia and tachypnea while maintaining SpO_2 of 80% on room air. Chest examination revealed scattered crackles involving bilateral infrascapular areas. There was no pallor, clubbing, icterus or generalized lymphadenopathy, however, peripheral cyanosis was present. Investigation conducted in Udhampur showed, mild transaminitis (SGOT- 58 IU/L, SGPT-135 IU/L) and LDH of 1651IU/L. Other investigations showed CRP-4.2mg/dL, D-Dimer-1425mg/ml (ref-<500mg/ml), FDP+(1:2), procalcitonin-0.14, NS1Ag for dengue, ELISA for HIV and Peripheral smear (PS) for malaria were negative. Arterial blood gas analysis showed hypoxemic respiratory failure. PS did not show features of bacteremia in the forms of shift to left or toxic granules. Blood & urine cultures were sterile. Chest X- Ray revealed nonhomogenous opacities in right middle and lower zones (Fig 1a). CECT chest showed patchy consolidation involving all lobes of right lung and left lower lobes with 'tree in bud' appearance (Fig 1b).

Course in the Hospital

Patient was managed as a case of atypical pneumonia with broad spectrum antibiotics (Piperacillin + Tazobactum, Clarithromycin, Teicoplanin, Clindamycin and Doxycycline) combined with T. Oseltamavir, for clinical suspicion of H_1N_1 infection. In addition to these, he was placed on non-invasive ventilation (NIV) & supportive care. He showed poor response to treatment with worsening dyspnea, cough, hypoxemia and persistent fever. He was air evacuated to tertiary care hospital in Delhi on day 6 of illness to our hospital with respiratory distress in form of tachypnea, hypoxemia (SpO_2-80% on room air which increased to 90% with NIV), nasal flaring, intercostal indrawing and use of accessory muscles of respiration. Chest examination revealed bronchial breath sounds in right infrascapular regions.

He had a rapid downhill course and progressed on to develop Acute respiratory distress syndrome (ARDS) [(Fig 3: (Serial Chest X-rays), Fig 4: (Serial ABG's)]. The TLC initially remained low and transaminitis persisted. [Fig 5] All investigations including sepsis panel test, bronchoalveolar lavage and blood cultures for bacteria were negative. Urine for pneumococcal and legionella antigen were negative. Viral markers were studied using Fast track diagnostics respiratory 33 kit. Fast track diagnostics respiratory 33 is a multiplex PCR based kit and contains primers for various organisms responsible for pneumonia including bacteria (Chlamydia pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae type B, Staphylococcus aureus, Moraxella catarrhalis, Bordetella spp., Klebsiella pneumoniae, Legionella pneumophila), Mycoplasma (Mycoplasma pneumoniae), fungi (Pneumocystis jirovecii) and viruses (influenza A, influenza B, influenza C, influenza A (H1N1) swl, parainfluenza viruses 1, 2, 3 and 4, coronaviruses NL63, 229E, OC43 and HKU1, human metapneumoviruses A/B, rhinovirus, respiratory syncytial viruses A and B, adenovirus, enterovirus, parechovirus, bocavirus).

He was intubated & placed on mechanical ventilation on Day 6 of illness, followed by inotropes and vasopressors. He was started an Inj Meropenem, Inj Vancoycin, Cap Ribavarin & Inj Methyl Prednislone, as a desperate measure, on day 7 of illness. The condition had worsened by day 8 of illness. He had become anuric requiring dialysis. He was not maintaining saturation on mechanical ventilation & Extracorporeal membrane oxygenator (ECMO) was started. Despite all the measures, the patient succumbed to his illness on day 9 of illness. His children who had suffered from fever with URTI symptoms had responded to conservative management.

Post mortem findings form lungs revealed foci of lobar pneumonia with destruction of alveolar septae, extensive formation of hyaline membranes (R>L, RUL>RMZ/RLL) and features suggestive of viral cytopathic changes in the form of virocytes with intranuclear inclusions and multinucleated giant cells. In addition, features suggestive of myocarditis, hemophagocytosis and acute tubular necrosis were also seen. However, the molecular analysis performed for causative organisms implicated in atypical pneumonia were negative (Fig 2).

Discussion

Highlights of the case

A young moderate smoker (SI-225), who after a short visit to Andaman and Nicobar Islands developed high grade fever, cough with scanty mucoid sputum, frequent passage of stools, dyspnoea, malaise and anorexia. His children also mounted the similar symptoms but of less intensity. He remained hypoxemic despite mechanical ventilation. His initial WBC count was normal and had raised transaminases and LDH. The procalcitonin was low and his radiological picture was of atypical pneumonia.

Was history of travel to Andaman significant?

Recent travel to Andaman is important clue as long travel with increased chances of exposure to respiratory pathogens in transit or in the islands, being tourist destination. The flora and fauna of Andaman is varied and different from mainland likely leading to

exposure to rare unknown diseases. Presence of similar complaints in children indicates common exposure.

Was our diagnosis correct?

Pneumonia is defined as symptoms of an acute lower respiratory tract illness (cough with or without expectoration, shortness of breath and pleuritic chest pain) for less than 1 week; with at least one systemic feature (temperature >37.7°C, chills, and rigors, and/or severe malaise); and new focal chest signs on examination (bronchial breath sounds and/or crackles) and new radiographic shadowing on imaging, in absence of any other explanation for the illness.[1] Our patient had all the features diagnostic of pneumonia. Patient was suspected to have viral pneumonia, a subtype of atypical pneumonia – an imprecise term usually accepted among clinicians, based on his clinicoradiological profile and is a diagnosis of exclusion. (Table1).[2]

Viral pneumonias may have widespread or focal and segmental pulmonary involvement with nonspecific clinical symptoms. Cough is usually dry and negative for bacterial cultures. WBC is usually normal or only slightly elevated, CRP is low and the imaging findings are also variable and overlapping. Common respiratory viruses causing pneumonia are described in table 4.[3-14]

Despite all the clinic-pathological-radiological features suggestive of viral pneumonia likely coronavirus, was found negative when tested for common respiratory pathogens using Fast track diagnostics respiratory 33 kit. This is not uncommon. EPIC study, a prospective multicenter population-based active surveillance study was carried out by CDC in US from 2010 to 2012.[15] It included 2259 adults requiring hospitalization for CAP.

The causative organisms identified were viruses (23%), bacteria (11%), bacteria and viruses (3%), fungi or mycobacteria (1%) and no etiology was made in 62% cases. The most commonly identified organisms were Rhinovirus (9%), influenza virus (6%), and S. pneumoniae (5%). There are very few Indian reports on the etiological agents of CAP. In a study of blood cultures performed in CAP, S. pneumoniae (35.3%) was the most common isolate, followed by Staphylococcus aureus (23.5%), Klebsiella pneumoniae (20.5%), and Haemophilus influenzae (8.8%).[16] An earlier study also found Str. pneumoniae to be the most common cause (35.8%), but it also reported Mycoplasma pneumoniae in 15% of the microbiologically positive cases.[17] Legionella pneumophila is an important cause which is often not considered in the Indian setting. In a recent study, 27% of patients with CAP were serologically positive for this organism and around 18% demonstrated L. pneumophila antigenuria.[18] Mycoplasma was found to be the etiological agent in 35% of cases.

There are no large studies that have specifically addressed viruses as the cause of CAP apart from pandemic influenza H1N1 virus. However, in all these studies, in majority of cases no cause was detected. Viruses were never analyzed in all these studies and that's a general trend. In India we rarely diagnose viral pneumonias. Likely the cases with no cause found were of viral pneumonias. The same is seen in comprehensive data on etiological agents for CAP wherein no case of viral pneumonia is reported from Asian countries wherein US and UK have approximately 30% cases of viral pneumonias.

The limitation of availability of viral markers and difficulty in culturing viruses may be an important factor limiting diagnosis of viral pneumonias. In addition, frequent occurrence of shifts and drifts renders molecular detection of involved viral speciation difficult. Moreover, Viral infections are self-limiting, which obviates the requirement for definitive diagnosis of viral infections. Availability of therapeutic regimens for viral infections is limited. CDC recommends Oseltamivir, to be given all suspected or confirmed influenza patients, requiring hospitalization or progressive, severe or complicated illness at the earliest, regardless of previous health or vaccination status.

Amanatadine/ Rimantadine is the suggested drug for Influenza A viral infection while Ribavirin acts on Coronavirus and Hantavirus group of viruses. Ganciclovir /cidofovir is recommended for Adenovirus infection (in vitro). Thus, with limited treatment options, diagnosing same is no big charm. Viral pneumonias although common, are rarely diagnosed and reported in literature of developing countries.

List of Tables and figures

Table 1. Arterial blood gas analysis

	7/11/16	10/11/16	11/11/16	12/11/16	13/11/16	14/11/16	15/11/16
SPO2	80% (room air) 90%(with O2)	80% (room air) 90%(with O2)	91% (with O2)	93% (with 02)	87-93% (endotracheal intubation)	90%	86%
pH	7.5	-	7.32	7.35	7.31	7.31	7.26
pO2	25.1	-	94.3	59.8	71.3	49.3	42.3
PCO2	36.3	-	41.8	33.4	65.3	60.7	36.6
HCO3	29.5	-	21.2	25.6	32	30.1	16
Impression	Respiratory alkalosis	-	Metabolic alkalosis	Respiratory acidosis	Compensated Respiratory acidosis	Compensated Respiratory acidosis	Metabolic acidosis

Table 2. Hematological, biochemical and immunological investigations

	07/11/16	**08/11/16**	**09/11/16**	**10/11/16**	**11/11/16**	**12/11/16**	**13/11/16**	**14/11/16**	**15/11/16**
Hb (gm/100ml)	16.5	14.9	-	15.1	14.6	15.0	13.3	12.6	13.5
TLC (cells/cumm)	9800	6900	-	**3450**	3850	6080	6300	8100	**13,430**
DLC	P86L11E01 M02	P84L13E 01M02	-	P69L24M 6E01	P70L22M6 E02	P74L16	P85L06M09	P92L06M02	P86L10M 04
Platelets (cells/cumm)	1,68,000	1.50,000	-	1,31,000	1,34,000	1,88,000	2,29,000	2.03,000	1,30,000
Urea/BUN (mg/dl)	34/-	24/-	20/-	-/11	-/12	-/10	-/10	-/20	-/107
Creatinine (mg/dl)	0.9	1.0	0.8	1.06	0.92	0.7	0.8	1.6	6.57
Na (meq/l)	141	133	132	131	136	137	137	124	159
K (meq/l)	3.9	3.5	3.7	3.9	4.1	4.2	4.7	4.5	4.7
Total Bilirubin (mg/dl)	0.7	0.5	0.7	0.5	0.5	-	0.4	-	1.3
AST (IU/l)	135	213	398	635	650	628	435	338	413
ALT (IU/l)	58	70	120	246	313	217	166	141	131
LDH	1651	-	-	-	-	-	-	2150	-
Total Protein (g/dl)	3.8	5.8	6.1	5.8	5.7	5.1	5.80	-	5.0

PT	13/15.8	13/15.8	-	13/14.7	-	-	-	-	13/20.1
INR	1.2	1.2	-	1.16	-	-	-	-	1.72
Blood culture	-	-	-	Sterile	-	-	-	-	Sterile
Chikungunya serology	-	-	-	-	-	-	-	-	Negative
D Dimer	1425	-	-	2.92	-	-	-	-	-
S Procalcitonin	1.4	-	-	-	1.25	-	0.97	-	-
Typhidot	-	-	-	-34	-	-	negative	-	Negative
Dengue serology	Neg	-	-	-	-	-	-	-	Negative
Scrub typhus	-	-	-	-	Negative	-	-	-	-
Leptospira IgG/M	-	-	-	-	negative	-	-	-	-
Urine culture	Sterile	-	-	-	-	-	sterile	-	-
CRP(mg/dL)	4.2	-	-	-	-	-	59.1	-	-
ICT for MP	-	-	-	-	Negative	-	-	-	-
Tracheal aspirate	-	-	-	-	-	-	Acinetobacter baumanii	-	-
Brochoalveolar lavage	-	-	-	-	-	-		Acinetobacter baumanii	-
Endotracheal tube	-	-	-	-	-	-	Acinetobacter baumanii	-	-

Table 3. Differences in Typical and Atypical Pneumonia

	Typical	Atypical
Symptoms	Fever, productive cough, pleuritic chest pain	Extrapulmonary symptoms, preceding URI, dry cough
Lab Parameters	Leucocytosis, ESR CRP	Likely to be Normal
Chest radiograph	Lobar or segmental consolidation	Diffuse patchy, interstitial / ground glass opacities
Likely causative organisms	Pneumococcus, Staphylococcus, H. influenzae, Klebsiella, anaerobes & aerobic gram negative bacteria	Virus, Legionella, Mycoplasma, Chlamydia

Table 4. Subtypes of viral pneumonia

S. N	Virus	Clinical features	Lung involvement	Chest Imaging finding	Lung Histopathology finding	Diagnostic modalities	Treatment	Outcome In pneumonia
1.	**Influenza Virus**	Dry cough, rhinorrhea, pharyngeal pain	Rare, may progress to pneumonia	Multifocal areas of ground-glass opacity and consolidation	Diffuse alveolar damage with hyaline membranes formation	Immunological antigen detection. Molecular diagnostic techniques	M_2 inhibitors – Amantadine & rimantadine Neuraminidase inhibitors – Oseltamivir & zanamivir	Mortality is high in cases of H_1N_1 pneumonia in immunocompromised individuals
2.	**Respiratory Syncytial Virus**	URTI, otitis media (more children)	Bronchiolitis (45-90%) & pneumonia (40%) more in infants & children	Non specific	Non specific	Rapid Antigen detection	Ribavirin	Good
3.	**Adenovirus**	Flu like illness mainly in summers	Rarely fatal interstitial pneumonia mainly in military recruits	Reticulo – nodular opacities bilaterally	DAD, bronchial epithelial necrosis, interstitial pneumonia 'Smudge cells' containing large basophilic, intranuclear inclusions are characteristic	ELISA / IF : antigen detection NAAT – viral DNA Quantitative DNA levels in plasma	Gandclovir cidofovir & ribavirin	Poor prognosis
4.	**Parainfluenza**	Croup usually children	Rare	-	-	-	-	-
5.	**Hantavirus**	Prodrome of fever, chills & myalgias with abdominal discomfort upper resp tract symptoms are absent	Hantavirus pulmonary syndrome (HPS) – mild dry cough & proponing dyspnea	Pulmonary edema without consolidation	-	-	Supportive, Ribavirin	High mortality

6.	**Coronavirus**	SARS & MERS fever, chills, myalgias & occasional diarrhea.	Cough & dyspnea progressing on to respiratory failure	Unilateral / bilateral GGO's & interlobular septal and intralbules interstitial thickening	DAD, type II pvenumocyte hyperplasia, squamous metaplasia & multinucleated giant cells, henophagocytosis	Raised LDH, trans aminases, and creatinickinase with lymphopenia and thrombocytopenia. Sputum PCR detection. Serum antibodies titers	No antiviral agent	SARS – fatal (46%) more older adults. MERS – more fatal in individuals with comorbidities
7.	**Cytomegalovirus**	Infects immuno compromised mainly transplant recipients causing acute pharyngitis	-	-	-	-	-	-
8.	**Herpes simplex virus (HSV)**	HSV, causes URTI	Pneumonia in neonates (rarely) or in patients with burns, organ transplantation or immuno compromised	-	-	-	Nil	-
9.	**Measles**	Influence like illness	4-50% patients develop bronchitis, pneumonia or bronchiolitis	Multilobar reticulonodular opacities	-	-	Nil	-
10.	**Rhinovirus (RV)**	URTI	Pneumonia and bronchiolitis in infants & young adults		-	-	Nil	-
11.	**Varicella zoster**	URTI with rash	Viral pneumonia – one to six days after onset of rash in adults	Diffuse nodular (1-10mm) opacities which may resolve with miliary calcified nodules. Hilar lymphadenopathy, pleural effusions & peribronchial opacities are present	-	-	Intravenous acyclovir	-

Figure 1. Panel 1a. X Ray Chest

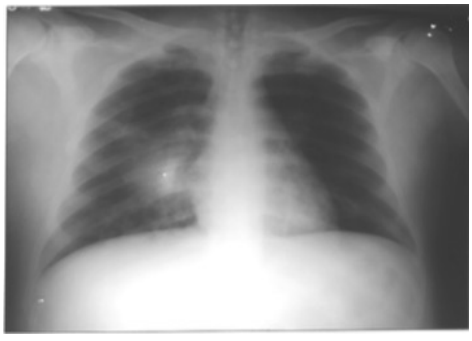


Figure1b. CECT Chest

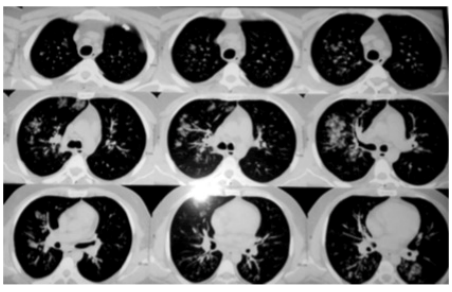


Fig 2a: Extensive haemaorrhage and destruction of alveolar wall

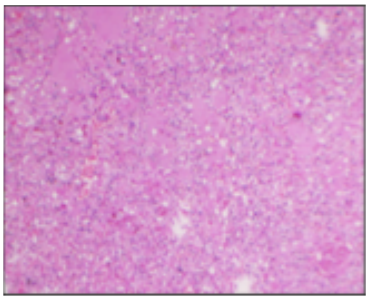


Fig2b: Extensive hyaline membreaneformation

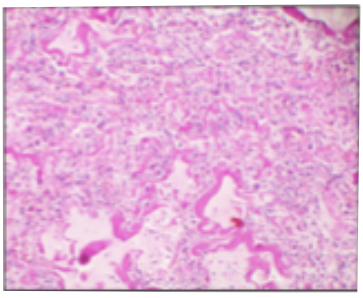


Fig 2c: Presence of virocytes

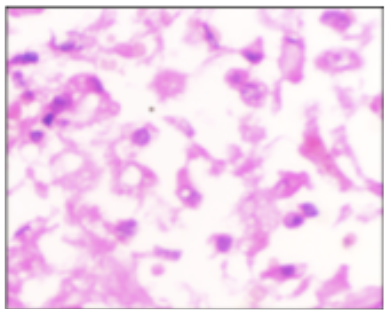
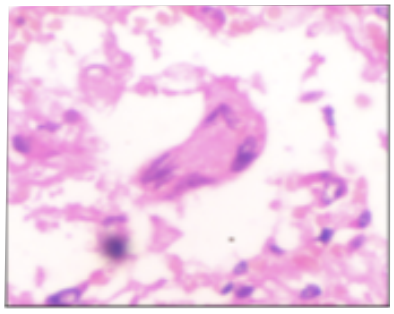


Fig 2d:Presence of multinuclcated giant cells



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