α. TNF-α is a potent pro-inflammatory cytokine, over-production of which has been implicated in mouse models of inflammatory arthritis and also in plasma and synovial fluid in patients with active arthritis including children with JIA. Thalidomide is also thought to suppress other proinflamatory cytokines including IL-6 [2,7], to down regulate adhesion molecules as well as to inhibit leukocyte chemotaxis and decrease the CD4/CD8 ratio [2,7]. Evidence concerning the use of thalidomide in SOJIA is limited [4]. In the largest of these studies, Lehman, *et al.* [4] and colleagues have reported the use of thalidomide (2 to 5 mg/kg/day) in 13 children with severe, refractory SOJIA. Six children were able to discontinue chronic steroids, thus highlighting its steroid sparing effect.

Thalidomide being a potent teratogen, birth-control is necessary for both males and females and extreme caution would be necessary when our patients achieve adolescent or child-bearing age. Another major though rare adverse effect is permanent peripheral neuropathy with long term use, for which, regular monitoring including physical (neurological) examination and nerve conduction velocity studies need to be performed [7]. We routinely enquire about the occurrence of tingling, numbness, paraesthesiae and perform a detailed neurological exam in all the three patients on every follow-up visit. So far we have not had reason to suspect peripheral neuropathy in any of our children.

Other side effects include sedation, somnolence, myalgia, constipation, neutropenia and anaphylaxis. The tolerability is generally found to be better with single night time administration. It is also highly economical, (approximate Rs 40/- per tablet of 50 mg the daily dose for a 15-25 kg child), which is in sharp contrast to the other reserve drugs available for this disease.

We advocate careful closely supervised use of thalidomide in consenting refractory cases of SOJIA where biologicals are unaffordable. Larger studies in our country on this 'poor man's biological' are in order.

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Decade Long Unexplained Anemia: Alert to ANCA Associated Vasculitis

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A 13-year old girl presented with a decade long anemia, diffuse alveolar hemorrhage and interstistial lung disease; was eventually diagnosed as ANCA associated vasculitis. High index of suspicion is thus warranted for alternative diagnosis in chronic anemia, despite increased prevalence of infectious diseases and nutritional anemia.

Key words: *Chronic anemia, Diffuse alveolar hemorrhage, Interstitial lung disease, Microscopic polyangitis.*

Diffuse alveolar hemorrhage (DAH) refers to accumulation of intra-alveolar red blood cells originating from alveolar capillaries due to underlying injury to alveolar microcirculation. The clinical picture includes hemoptysis, anemia, hypoxemic respiratory failure with infiltrates on chest *X*-ray [1,2]. In the absence of infections or any hemodynamic cause for DAH, anti-neutrophil cytoplasmic autoantibodies (ANCAs) must be looked for and ANCA-associated vasculitis (AAV) - mainly microscopic polyangiitis (MPA),Wegener granulomatosis, or Churg-Strauss syndrome should be considered. We report a case of MPA who presented with DAH and was further found to have interstitial lung disease (ILD).

CASE REPORT

A 13-years-old girl presented with increasing pallor and gradually worsening dyspnea for last 15 days. She had history of recurrent anemia since the age of two years, requiring multiple (four times) blood transfusions. She had intermittent episodes of cough, fever, arthralgia, anasarca, and dyspnea on exertion for last 10 years. There was no history of bleeding from any site. She had received antitubercular therapy (6-months course) one year back, prior to presentation at our hospital. Her birth, development and family history was non-contributory.

On examination, her heart rate was 142/min, respiratory rate 48/min, blood pressure 102/60 mmHg and SpO_2 was 92% on room air. She had severe pallor, grade-3 clubbing, and non-blanchable erythematous papular rash over both feet. Chest examination revealed subcostal and intercostal retractions with fine crepitations audible all over the chest. Hepatosplenomegaly was present. Growth was well preserved. Rest of the systemic examination was normal.

Laboratory Investigations: Blood investigations revealed anemia (hemoglobin 3.3 g/dL), platelets 120×10^3 /mm^3, total leukocyte count of 5400/mm^3 with normal differential count. Past and present radiographs showed prominent interstitial reticular shadows in the middle and lower zones (***Fig.*1**). HRCT chest showed diffuse ground glass opacities in bilateral lung fields and interstitial infiltrates with honeycombing especially in the lower zones (***Fig.*2**). Lung function tests showed moderate restriction pattern: forced vital capacity was <64% predicted), and early small airway obstruction (mean peak expiratory flow rate was <70% predicted). Echocardiography revealed mild pulmonary artery hypertension with moderate tricuspid regurgitation. Prussian blue staining of sputum for hemosiderin-laden macrophages was positive with siderophage percentage more than 86 % corresponding to Golde score >100, confirming DAH [1]. Urine microscopy and renal function tests were normal. ANCA was positive by immunoflourescence with a perinuclear staining pattern and ELISA for antimyeloperoxidase ANCA (MPO-ANCA) was positive (2.808, cutoff-0.394).

Common infections like malaria, enteric fever, tuberculosis were ruled out on investigations. Her ANA and dsDNA were negative. AntiGlomerular Basement Membrane Antibody and Anti Phospholipid Antibody

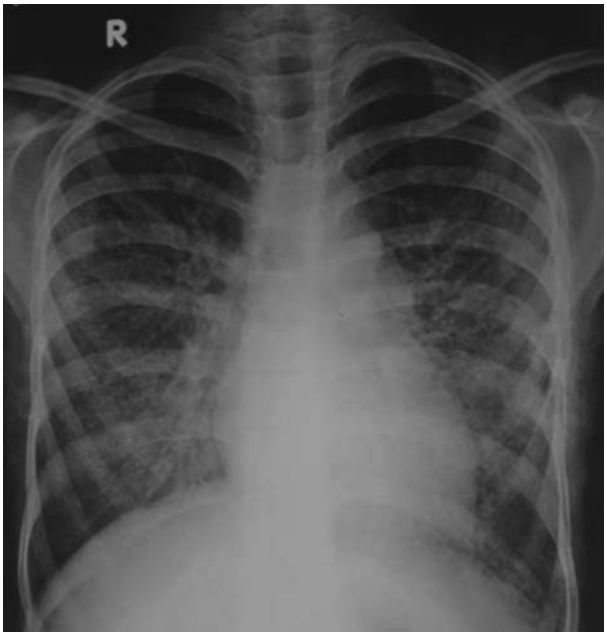

FIG.1 *Chest X-ray shows prominent interstitial reticular shadows due to diffuse alveolar hemorrhage.*

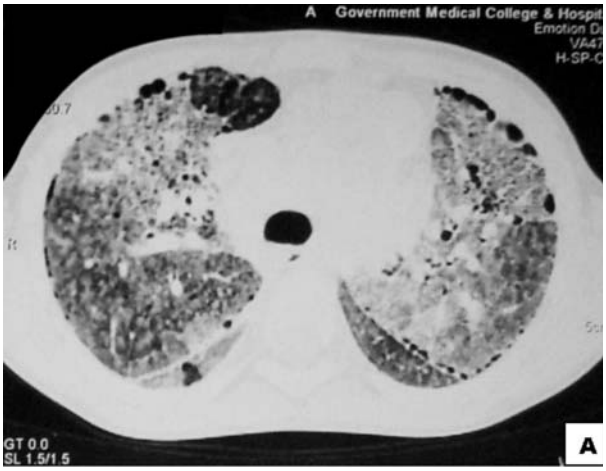

FIG.2 *HRCT of lungs show bilateral ground glass opacity and interstitial infiltrates with honeycombing especially in the periphery.*

workup were negative. Serology for Human Immunodeficiency Virus, Hepatitis B surface antigen, Hepatitis C and tissue transglutaminase antibodies were negative. Serum IgE levels were normal (150IU/mL). Direct Coombs test was negative. Skin biopsy was unremarkable and did not reveal features of leucocytoclastic vasculitis.

In view of the multisystem involvement and positive serology for MPO-ANCA, a diagnosis of MPA was made. She was started on oral steroids 2 mg/kg/day and supportive therapy. She went into remission on oral steroids. After 6 weeks, daily therapy was shifted to alternate day and then tapered over one year. Simultaneously, azathioprine was added.

She is on regular follow-up for one year. She had one relapse in past year which was managed with short course of steroids. She has remained normotensive, hepatosplenomegaly has regressed, has had no urinary complaints or need for blood transfusions (hemoglobin-13.1g/dL), normal repeat renal functions and, Elisa for MPO-ANCA has returned to normal.

DISCUSSION

Severe unexplained anemia in a female with progressive dyspnea and alveolar opacities on chest imaging, without hemorrhage elsewhere alerted us to the possibility of DAH. Long history of fever, cough, clubbing, hepatosplenomegaly, led to the possibility of ILD. Absence of cutaneous/mucous telangiectasias clinically ruled out hereditary hemorrhagic telangiectasia. Nonspecific constitutional symptoms, DAH, ILD with sparing of the upper airways, no asthma/eosinophilia with positive MPO-ANCA clinched the diagnosis of MPA.

MPA is a non-granulomatous pauci-immune primary systemic vasculitides which affects small vessels. Kidneys and lungs are the most frequently affected organs. Annual incidence rates of MPA is 2.1-17.5 per million [3]. DAH and ILD have both been reported in MPA [4,5]. However, unlike our case, untreated MPA usually are rapidly progressive and fatal [4]. Though DAH in MPA is usually acute, rarely DAH has been reported as part of chronic MPA in adult patients [6]. The index case had a slow indolent course with frequent exacerbations which has previously not been reported in a child. Incidence of ILD is 7.2% in MPA. Diagnosis of ILD is usually based on radiological evidence on HRCT and/or lung function tests [5]. Generally, lung biopsy is not recommended for diagnosis [1,2]. It is considered if DAH is associated with negative serology and not a part of a systemic disease. Notably our case didn't have renal involvement in past 10 years [1,2].

Two main mechanisms have been proposed for the development of ILD in patients with small vessel vasculitis. Firstly, the pulmonary fibrosis occurs in response to pulmonary haemorrhage and secondly, the ANCA antigens such as MPO undergo translocation to the surface of neutrophils (possibly in response to proinflammatory cytokines), and subsequent binding of circulating ANCA results in neutrophil degranulation and release of reactive oxygen species, causing injury and consequent fibrosis [7,8].

Treatment typically includes corticosteroids, immunosuppressive agents, and occasionally plasma-pheresis. 90% of patients achieve remission at 6 months. Relapse rates in AAV are 50%; severe organ-threatening damage and treatment-related adverse effects occur in 25% of patients. 10% of those refractory to standard immunosuppressant therapies are at high risk for death [9]. Serial hemoglobin measurement guides on DAH control or progression [1]. Disappearance of ANCA is almost always associated with absence of disease activity [10].

We conclude that DAH should be considered as a differential diagnosis in recurrent unexplained anemia. A high index of suspicion and prompt management can reverse the symptoms quickly.

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Respiratory Flutter Syndrome in a Neonate

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Respiratory flutter or diaphragmatic flutter is a rare disorder characterized by involuntary, high frequency contractions of the diaphragm. Only 7 cases are reported in infants till date. The present case presented with life threatening respiratory distress immediately after birth. In view of high respiratory rate of 120-154 per minute, clinical and fluoroscopic evidence of diaphragmatic contraction and absence of any obvious CNS, cardiovascular and respiratory pathology, respiratory flutter was diagnosed. It was also associated with dysphagia and laryngomalacia. The patient was managed with prolonged continuous positive airway pressures (CPAP) with partial success, but symptoms improved with use of chlorpromazine.

Key words: *Diaphragmatic flutter, Newborn, Respiratory distress.*

Respiratory or diaphragmatic flutter (DF) is a heterogeneous neurologic disorder, rarely reported in neonates, infants and children. It is characterized by rapid, involuntary high frequency contractions of the diaphragm (35-480/min), often superimposed on normal diaphragmatic excursion; and considered to be a form of myoclonus [1-3]. The reported respiratory patterns of DF are highly variable. It may occur in inspiration, expiration or in both phases of respiration, generally asynchronous with heart rate and usually resolves during sleep, but may persist within all stages of sleep. The duration of DF may vary from days to 18 years but typical to this disease, gas exchange (CO_2 and O_2) abnormalities are absent. Since the first case report in 1723, a case of self diagnosis by Leeuwenhoek [4], only 7 cases are reported in infants [2, 3, 5]. We report an infant with diaphragmatic flutter associated with dysphagia and laryngomalacia.

CASE REPORT

This full term male baby was delivered by elective caesarian section with birthweight of 3100g to a non-consanguineously married 23 years old primipara with no antenatal risk factors and normal antenatal ultrasound scans. Baby cried immediately after birth. At 2 hours of life, baby was shifted to NICU for excessive drooling of saliva and respiratory distress. Baby was intubated and ventilated at the referral NICU for 5 days, but in view of extubation failure twice, he was referred to our unit on 6th day of life. On examination, baby was hemodynamically stable and systemic examination was normal. He was lethargic, tone, and reflexes were poor, and pupils were normal. Baby was ventilated on SIMV mode, weaned and extubated to CPAP over next 48 hours. During ventilation, his respiratory rate was very high, irrespective of SIMV rate and level of sedation. In view of history of extubation failure, retrognathia and excessive pooling of secretions and recurrent upper lobe collapse of lungs, airway evaluation was done. Direct laryngoscopy revealed moderate laryngomalacia and omega shaped epiglottis; bronchoscopy was normal. Expanded newborn screening with immunoreactive trypsinogen (IRT) was normal. MRI brain, nerve conduction study and electromyography were normal. Sepsis work-up was negative. 2D echo cardiography was normal. During CPAP, respiratory distress persisted with a biphasic pattern of respiratory rate ranging from 40 – 154 per minute. Excessive secretions and respiratory distress was persistent even after 10 days of CPAP use. During clinical observation, it was noted that baby was "appearing frightened". Respiratory rate monitored with impendence plethysmography (Philips Intellivue MP 40