Letters to Editor
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Kidney Tubular Cell Protection; Recent Findings

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Acute renal failure (ARF) or acute kidney injury (AKI) may develop due to numerous factors including obstruction of the urinary tract, toxic substances to kidney and low blood volume[1-3]. Acute renal failure may lead to numerous complications including metabolic acidosis, uremia and changes in body fluid balance. The diagnosis of acute kidney injury is based mainly on the laboratory findings, such as blood creatinine and urea nitrogen. Management includes treatment of the underlying disorder and supportive care[4-8]. Recently, attentions are mostly on protection or prevention as well as accelerating the regeneration of tubular cells against injurious insults to the kidney. To study acute kidney injury, various models have been defined for each specific condition. Gentamicin (GM) which is an aminoglycoside antibiotic and is derived from gram-positive bacteria, has a potential for the treatment of aerobic gram-negative infections. Gentamicin is extensively used for induction of ARF in preclinical studies and evaluation of renal protective agents. Gentamicin is usually accumulated in kidney proximal tubular cells which may trigger renal injury, leading to brush border network damage[9,11]. The kidney toxicity is usually caused by increased free radical production, suppression of antioxidant defense mechanisms as well as acute renal tubular cells necrosis[9-12], which lead to kidney dysfunction and diminished glomerular filtration rate (GFR). The pathological mechanisms include increase in endothelin-1 augmentation of oxidative stress, upregulation of transforming growth factor-beta (TGF-β), apoptosis, significant increase in monocyte/macrophage infiltration into the renal cortex or medulla and eventually necrosis[10-15]. Gentamicin has also been shown to increase the generation of reactive oxygen species (ROS), hydrogen peroxide, superoxide anions and hydroxyl radicals in proximal tubular cells, leading to kidney damage[9,10]. Therefore, scientists usually focus on the use of various antioxidants for the treatment of gentamicin renal toxicity[9,10]. In this regards, the role of antioxidants in mitigating the gentamicin renal toxicity protection, tubular effects and integrative glomerular and possible interplay have been described. Oxidative stress is induced by an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or decrease in body antioxidants. Indeed it is usually described as an imbalance between the level of production and removal of cell oxidants. This imbalance causes a decline in the ability of biological systems in detoxification of the reactive intermediates or repair of the resulting damage. Therefore, in gentamicin administration in should be noted that it might induce severe renal toxicity. The renal toxicity of gentamicin is high enough to be used in the study of drug-induced acute kidney damage. In fact, acute renal toxicity is a common clinical entity with high mortality and morbidity rates which has been attributed to induction of oxidative stress in the kidney[8-11]. Renal toxicity may also be induced by other complications like diabetes, chronic renal failure or vascular complications, all of which induce oxidative stress and hence put the patients at higher risk of acute renal failure due to ischemic and nephrotoxic insults[11-15]. Medicinal plants which mostly possess a lot of phytochemicals with antioxidant properties have been recently in the focus of researchers and scientists for treatment and prevention of various oxidative stress-related complications[8,16,17]. These plants have anti-oxidant activities due to phytochemicals including phenolic and carotenoid compounds[16-19]. Phenolic compounds are abundantly presented in herbal medicines and food products and mainly consist of flavonoids, anthocyanins, phenolic acids and tannins with antioxidant activities[16-21]. These

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compounds and carotenoids have been shown to reduce the risk of several chronic and degenerative complications[19]. Kidney damage induced by oxidative stress is associated with increased ROS/RNS production which is significantly prevented by these compounds[8,18-24]. Medicinal plants antioxidants elaborate endogenous antioxidants capacity to protect renal damage by reduction of lipid peroxidation (LPO)[17-23]. Tocotrienol, a member of vitamin E family with antioxidant activity, supplementation has been shown to increase catalase activity and glutathione level and reduce renal LPO, resulting in proximal tubular injury[18-24]. Furthermore, it has been able to improve the index of NO_2-/NO_3 generation. Tocotrienol has also been shown to protect the renal injury induced by potassium dichromate [19-26]. Ligustrazine, an alkaloid extracted from *Ligusticum wallichii* with antioxidant activity, was able to protect the kidneys from ischemia/reperfusion injuries by decreasing ROS generation, reducing MDA, and elevating SOD activity[20-23]. Troxerutin, abundantly found in tea, coffee, cereal grain and a variety of vegetables and fruits, has been shown to reduce oxidative stress-induced kidney damage[23-25]. It is able to reduce malondialdehide level and enhance antioxidant enzyme activities, including catalase, SOD, GPx, and Cu/Zn[18-26]. As mentioned above, antioxidants mechanism of action is giving electrons to free radicals and trying to turn them neutral. People who intake low vegetables and fruits are at greater risk of developing some complications compared to others. Although free radicals are known to contribute to kidney injury, nephrotoxicity[26,27], hepatotoxicity, diabetes, heart disease[19-27], atherosclerosis[20-28], vision loss and cognition complications[21-30], and abundant researches, particularly laboratory trials, have shown the beneficial effects of antioxidants against these complications, long term clinical trials do not uniformly confirm this matter. This is especially true for single antioxidant therapy. It seems that the molecules found naturally in grains, fruits and vegetables, usually act to prevent a variety of complications like kidney and liver injuries, but not all antioxidants in different conditions act the same[26-30]. The result evidences related to the consumption of single antioxidants such as vitamin E or vitamin C are contrary[16,17, 26-30], however ameliorative effect of vitamin E against cisplatin-nephrotoxicity in our previous study was obsereved[31]. Similarly, ameliorative property of vitamin E and vitamin A on the protection of kidney scarring in children with acute pyelonephritis was also obsereved by Sobooti et al[32]. Also, findings about the consumption of antioxidant combinations are not entirely clear. However, it seems that natural products, especially fruits, vegetables and grains are more reliable in protecting kidney complications[16,17,26-34]. Likewise Ashtiyani et al found, grape seed extract abolishes kidney disturbances following reperfusion in rats in their recent study[35]. In this regard, the lack of beneficial effect of a single or even a combination of antioxidants is not clear. What is clear is that antioxidants system in the body is complex and antioxidants usually act as parts of complicated networks. Therefore, a single antioxidant cannot do the same as the whole[8,16,17,30-33]. Although it has been shown that eating grains, fruits, grains and vegetables, which are rich in antioxidants, provides protection against oxidative stress induced complications such as kidney and liver injuries, however, this does not mean that antioxidants will prevent or cure the problem, especially not when they are taken out of their natural context[8,16,17,30-33].

Oxidative stress contributes to kidney damage by increase of oxidative stress, particularly insufficiency of endogenous antioxidant defense system. Medicinal plants antioxidants have been demonstrated to prevent oxidative induced kidney damage by reduction of lipid peroxidation and increase in scavenging ability of antioxidant defense system. Consumption of medicinal plants antioxidants seem to be important remedies to abrogate pathology of oxidative stress induced kidney injury, but single and even combination of antioxidants do not act the same as whole natural products.

Key words: Acute Renal Failure; Acute Kidney Injury; Medicinal Plants; Oxidative Stress; Reactive Oxygen Species

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Extramedullary Hematopoiesis in Adrenal Gland. An Uncommon Cause of Adrenal Incidentaloma in Sickle Cell Disease

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Dear Editor

Extramedullary hematopiesis (EMH) is a response to insufficient blood cell production by producing of blood elements outside of the marrow cavity. It occurs most often due to hemolytic anemias such as thalasemia, hereditary spherocytosis and sickle cell anemia. It also could be seen in prolonged iron deficiency anemia, myelofibrosis, polycythemia, leukemia and lymphoma[1,2,3].

EMH occurs most commonly in the reticuloendothelial system such as spleen and liver, but it may also be seen in organs, such as bowel, breast, brain, pleura and adrenals[2,4].

In our review of literature we found reports of adrenal gland EMH in patients with beta-thalasemia, agnogenic myeloid metaplasia and hereditary spherocytosis. EMH in sickle cell anemia has been reported in paranasal sinuses, mediastinum and retroperitoneum.

Here we report a case of adrenal gland EMH as adrenal incidentaloma in a patient with sickle cell anemia; in literature review no similar result is found[1-8].

The patient was a 15 year-old female with homozygous sickle cell disease. She was diagnosed as a case of sickle cell at the age of two years when she presented with bone pain. After that she was under routine clinical follow-up. She had history of multiple painful bone crises and one episode of acute splenic sequestration in childhood. During hospital course she complained of vague abdominal and left flank pain. In physical examination, findings were normal vital signs, pale conjunctivae and skin with mild soft hepatomegaly. No abdominal tenderness was noticed. No supra renal mass was detected on physical examination. Routine work/up for evaluation of abdominal pain was done.

Laboratory investigation showed hemoglobin 11 g/dL, WBC count 1.0×10^9/ L, platelet count 390×10^9/ L, MCV 70.1 fl, MCH 21.6 pg. Biochemical investigations were: serum bilirubin 1.8 mg/dL; conjugated bilirubin 0.8 mg/ dL, blood urea 27 mg/ dL, serum creatinine 0.7 mg/dL, serum calcium 8.2 mg/ dL, serum phosphorous 6.6 mg/dL, fasting blood sugar 100 mg/dL; alanine aminotransferase 41 IU/ dL, aspartate aminotransferase 50 IU/dL. Tests for hepatitis C virus (anti HCV antibody) and HIV antibodies (Anti HIV-1,2) serum HBsAg and HBc antibody were negative. Fasting serum cortisol level was 13 mcg/dL. Urinalysis was normal. Abdominal sonography showed mild hepatomegaly and a well-defined left suprarenal solid mass in size of 7.7×5.3 cm. Abdominal CT scan confirmed a 7cm well defined suprarenal mass (Fig 1).

Surgical plan was considered and left adrenal-ectomy done. On gross examination, a brown mass measuring 7×5×3 cm was detected, surrounded with a rim of normal adrenal gland parenchyma.

The definite diagnosis was confirmed with histopathology that revealed active hematopoiesis in adrenal gland (extramedullary hemopoiesis) (Fig. 2). Her postoperative course was uneventful and she was discharged from hospital in good condition.

Adrenal incidentaloma has a prevalence of 5% in the general population. EMH is a rare cause of incidentaloma and is seen in patients with hematologic disorders such as beta-thalasemia,

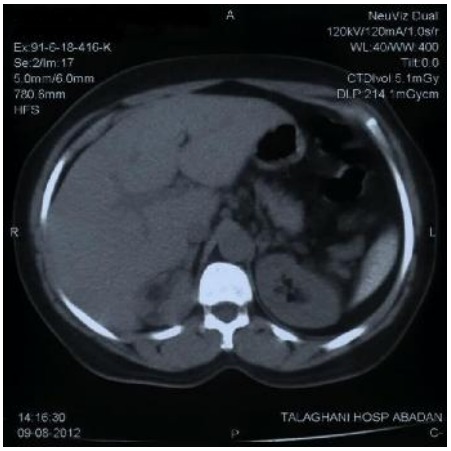

Fig. 1: Right supra renal mass.

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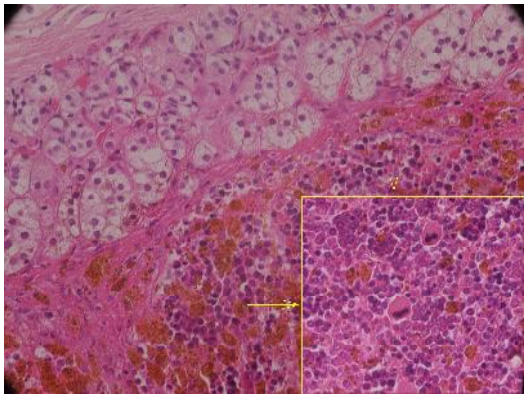

Fig. 2: Remnant of adrenal cortical tissue with foci of hematopoietic cells including erythro-myeloid, megakaryocytic cells with hemosiderin deposit (H&E ×400) (Yellow Arrow)

agnogenic myeloid metaplasia and hereditary spherocytosis.

EMH is a physiologic or pathologic compensatory mechanism that occurs because of imbalance between bone marrow erythropoiesis and circulatory blood demands. In histopathology, this intends to mimic a normal bone marrow with all marrow elements[1,2,3].

EMH occurs most commonly in the reticuloendothelial system, but it may also be developed in organs such as lungs, gastrointestinal tract, breast, brain and kidney and rarely in adrenal[4,5].

The exact mechanism of EMH in the adrenal gland is unknown, but several hypotheses are suggested. The adrenal gland has hematopoietic capacity during the fetal period and EMH may develop from primitive rests in diseased condition. Other scientists believe that embolization of hematopoietic stem cells and homing in adrenal gland may occur. Chronic hypoxia is another presumptive cause of EMH[3,6,7].

EMH is seen in hemoglobinopathies such as thalassemia, hereditary spherocytosis and in hematologic diseases including myelofibrosis and myeloproliferative disorders. In the literature, most cases were associated with intermediate thalassemia. The frequency of extramedullary hematopiesis in thalassemia major was very low, especially, when ineffective erythropoiesis was suppressed by regular transfusion. In infrequent transfusion, chronic hypoxia and subsequently EMH develops[4,5,8,9]. EMH is rare in patients with sickle cell disease. Although few cases of intrathoracic, pelvic and paranasal have been documented in literature[8,9], our case was the first one reported as adrenal incidentaloma.

EMH is usually asymptomatic and discovered incidentally. Symptomatic cases occur due to mass effect with compression to adjacent organ[8,9]. The surgical indication for excision of the adrenal incidentalomas is the tumor size. Adrenal tumor larger than 6 cm in diameter must be excised. In these cases, the risk of adrenal cancer is 35% to 98%[8,9].

Treatment options for patients with EMH are described for thalassemia patients and depend on the location and symptoms. Different approaches included surgery, local radiation, blood transfusion and hydroxyurea. Hydroxyurea stimulates the synthesis of hemoglobin F and therefore participates in inactivation and shrinking of EMH. This effect was documented in thalassemia diseases. For paraspinal/epidural lesions, directed low-dose radiotherapy is recommended[9]. In conclusion, extramedullary hematopiesis should be considered in the differential diagnosis of patients with sickle cell disease that present with a solitary mass. The CT-guided biopsy can exclude a true neoplasm and alter the management and prognosis.

Key words: Extramedullary Hematopoiesis; Sickle Cell; Adrenal Gland

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Chicken Meat Anaphylaxis in a Child with No Allergies to Eggs or Feathers

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Poultry meat is very popular in today's healthy diet. Despite the fact that chicken meat is widely consumed, allergy to chicken meat is rarely reported[1]. However, we present here a case of a child with chicken meat anaphylaxis, yet who has experienced no allergies to eggs or to feathers.

A fifteen-year-old male patient with a personal history of chicken meat allergy was referred to our clinic. Aged seven, he experienced angioedema of the lips, redness of the face and trunk, itching eyes, and hoarseness five minutes after he ate chicken meat. His symptoms gradually resolved without admission to hospital. Subsequently, he did not consume any chicken meat until last year (2013), when he reported nasal itching and irritability while passing by restaurants serving chicken doner kebab. Last year, he also reported similar complaints after consuming chicken wings. He was admitted to a public hospital where symptomatic treatment was given. He was advised not to eat chicken meat and continued to display similar symptoms whenever he failed to comply with the diet and did consume it. He never ate turkey, duck, or goose, and was tolerant to eggs. He had no physical contact with birds. His personal and family history was unremarkable, and he had no known drug allergies, including antibiotics. His physical examination was normal.

Laboratory results on admission: CBC with white blood cell differential was within normal range; serum total IgE was 351 IU/ml. Skin prick tests (SPTs) with commercial allergenic extracts of chicken (Alyostal Stallergenes, France), egg white, and egg yolk (ALK Abello, Denmark) were positive. SPT was negative for a feather mixture (Alyostal Stallergenes, France). Skin prick–prick tests (PPTs) were performed with raw and cooked chicken and turkey meat: they were all positive (Fig 1). Both SPTs with the same commercial allergenic extracts and PPTs with raw and cooked chicken meat were performed on four healthy, non-atopic adult volunteers, all resulting negative. The specific IgE serum level for chicken meat in our patient was 10.20 kU/L (Class III) (chemiluminescence immunoassay). An oral challenge test with chicken meat was not performed due to the risk of precipitating a severe reaction. The clinical history of our patient and the results of in vivo and in vitro tests were compatible with chicken meat allergy. We advised him not to consume any avian meats and prescribed an epinephrine autoinjector to use in case of anaphylactic emergency.

Allergic reactions to chicken meat are very rare[1]. The prevalence of chicken meat allergy in food allergic patients is 0.6%–5%[2]. Patients with chicken meat allergy can be separated into two

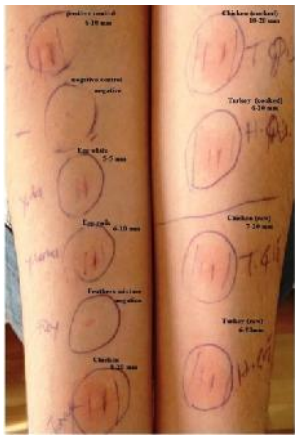

Fig. 1: Skin prick tests with commercial allergenic extracts of chicken, egg white, egg yolk, feather mixture, skin prick-prick tests with raw and cooked chicken and turkey meat

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groups: those who have chicken meat only allergy[1,3], and a second group, a subset of 'bird–egg syndrome' with allergies to chicken meat, egg yolks, and other bird allergens from serum and feathers[4,5].

The most reported symptoms of allergy to chicken meat are urticaria[6], oral allergy syndrome[7], and non-IgE mediated colitis[8]. A few cases of anaphylaxis due to chicken meat have been reported: allergy to chicken meat only beginning from childhood in two cases[6,9]; allergy to chicken meat only in two adults[1,3]; a single case report of a child with bird–egg syndrome[4]. Our case represents the third reported case of chicken meat anaphylaxis in children with no allergies to eggs or feathers.

In our patient, SPTs were found to be positive with commercial allergenic extracts of egg white, egg yolk, and chicken. However, he was able to tolerate eggs. His SPT with the feather mixture was negative. Gal d 5 (alpha-livetin) is believed to be the causative antigen of bird–egg syndrome[10]. Although IgE reactivity against Gal d 5 can be reduced 88% by heating[1], skin PPTs performed with both raw and cooked chicken and turkey meat were positive in our patient.

Recently, muscle alpha-parvalbumin and myosin light chain 1 (MLC) have been identified as new allergens in chicken meat allergy[3]. Unfortunately, we could not carry out a further investigation to determine allergenic components such as immunoblotting or mass spectrometry. However, the patient's tolerance of eggs led us to believe that allergens such as MLC might be the responsible antigens in our patient's case.

The causative antigen in chicken meat only allergy is not known for certain. Antibiotics given to chicken via chicken feed have been thought to be responsible[1]. However, our patient had no known antibiotic allergy.

The patient had never before consumed turkey. However, since IgE binding to alpha-parvalbumin and myosin has been identified in turkey meat[3], we advised him not to eat turkey meat due to cross-reactivity.

We have presented this case because of the rarity of allergy to chicken meat and because we wish to attract attention to chicken meat allergy without bird–egg syndrome.

Key words: Chicken; Meat; Anaphylaxis; Eggs; Feathers

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Unusual Presentation of Congenital Neuroblastoma as Persistent Respiratory Distress and Fever from Age of 13 Days in an Infant: A Case Report

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Dear Editor

Neuroblastoma, an embryonal tumor arising from the sympathetic nervous system, is the most common neonatal malignancy that accounts for >20% of neonatal cancers[1]. The most common location for neuroblastoma to originate (i.e., the primary tumor) is on the adrenal glands but

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primary cancer originating from lung is very rare. We report a case of newborn who was referred to us as case of persistent pneumonia but was diagnosed as primary congenital neuroblastoma of lung.

Baby Y, female infant was referred at age of 23 days with difficulty in breathing from age of 13 days. The infant was born by normal vaginal delivery with weight of 2.6 kg and Apgar of 7/8/8. Ante-natal period was uncomplicated with normal scans. Infant had fever (101˚ to 102˚ F) on and off from 13 days of age and respiratory distress for which baby was admitted in hospital. Baby received injectable antibiotics in referral NICU for 10 days. Baby was referred to us in view of persistence of respiratory distress and X-ray findings. At admission, the infant weighed 2.5 kg, had a temperature of 37.5°C, HR 148/min, RR 50/min, BP 64/42 mm Hg, mild to moderate subcostal and intercostal retractions, air entry decreased on right side, dusky peripheries, SpO_2 65% on room air, SpO_2 93% with oxygen by hood with flow of 5 liters/min, liver 2cm below costal margin, spleen 1cm below costal margin, pedal edema. Blood counts revealed neutrophilic leukocytosis (total count 18600/mm^3, neutrophils 66%), C-reactive protein -41.4 mg/l. Chest X-ray showed right upper lobe heterogeneous opacity and distal consolidation with right lower lobe showing patchy consolidation (Fig. 1).

Ultrasonography showed hepatosplenomegaly in abdomen and in chest showing intrathoracic soft tissue mass lesion in right paratracheal and upper lobe with distal consolidation of middle and lower lobe. The infant was started on intravenous antibiotics and supportive care. In view of persistence of respiratory distress repeat X- ray was done after 1 week which didn't show any improvement (Fig. 2). Chest CT scan showed posterior and apical segments of right upper lobe having consolidation without air bronchogram with small central cavitation. Anterior segments of right upper lobe and right middle lobe lateral segment showed nodular lesions. Right lower lobe basal segments showed areas of consolidation with curvilinear air lucencies with intercavitory bodies. Left lower lobe showed multiple confluencing nodular lesions with curvilinear air lucencies (Fig 3). CECT chest showed possibility of metastatic neuroblastoma and Fine needle aspiration cytology (FNAC) and biopsy was planned. FNAC was done which revealed moderate cellular cells which were mostly acute inflammatory cells with atypical tumor cells. Individual cells were round to polygonal cells having scanty to moderate amount of eosinophilic cytoplasm with anisopoikilocytosis with hyperchromasia, high nuclear to cytoplasmic ratio with prominent nucleoli. Biopsy showed small, round, blue cell tumor cells with high nuclear to cytoplasmic ratio and presence of Homer-Wright pseudo rosettes. Baby was started on chemo-therapy but infant succumbed to death after 10 days of starting treatment.

Congenital neuroblastoma is defined as neuro-blastoma identified within a month of birth[1]. Neuroblastoma is slightly more common in boys than in girls with a male to female sex ratio of 1.2:1[2]. Neuroblastoma is especially unique because of its varied presentation in the young. The tumor has been detected as an unexpected finding in the fetus either as a cystic or solid mass above upper pole of the kidney[3,4].

Neuroblastoma is characterized with densely cellular, primitive, "small blue-cell tumor" appearance. Undifferentiated neuroblastoma may

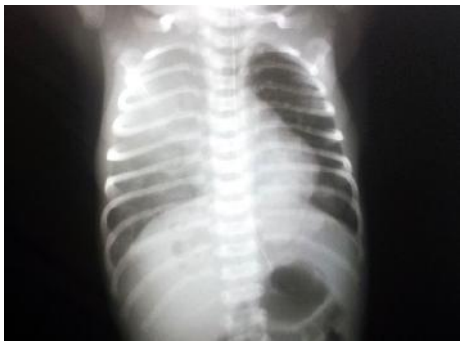

Fig. 1: Chest X-ray at admission

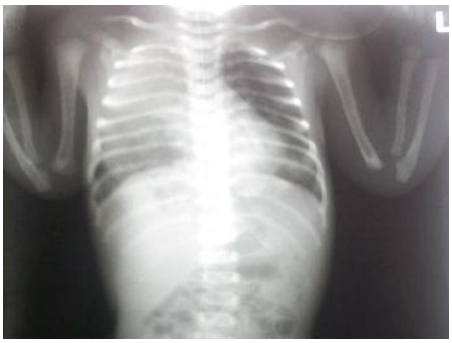

Fig. 2: Chest X-ray after treatment for 1 week

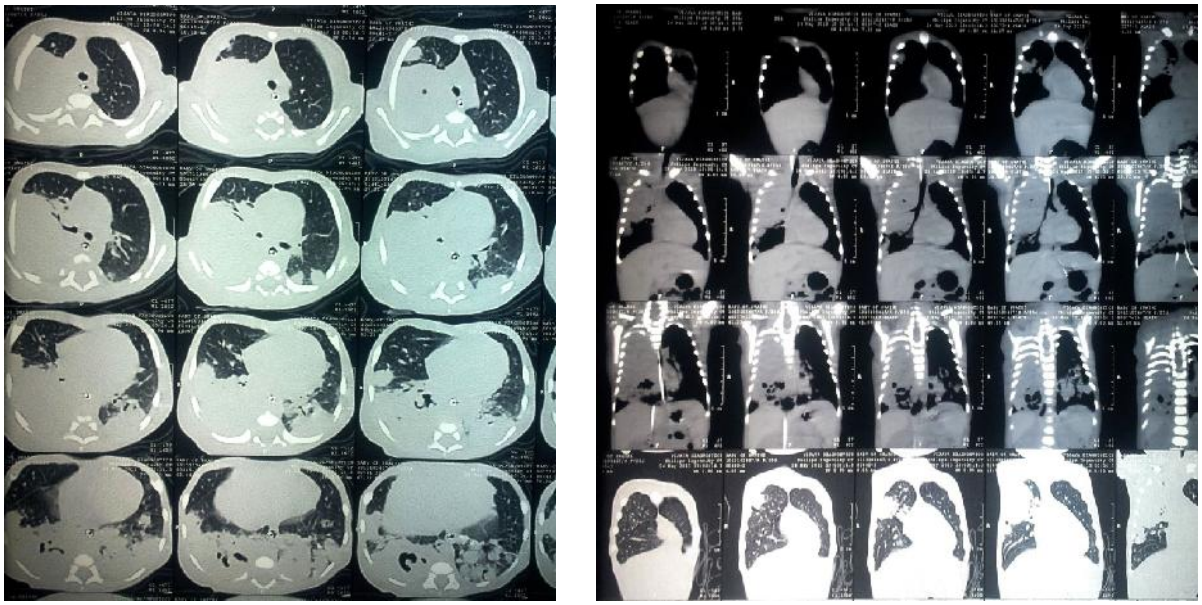

Fig. 3: Multiple confluencing nodular lesions with curvilinear air lucencies in Chest CT scan

be difficult to distinguish by electron microscopy from other small-cell malignant tumors. The predominance of blue staining is due to the fact that the cells consist predominantly of nucleus, thus they have scant cytoplasm[5]. The tumor cells are reactive for neuron specific enolase (NSE), synaptophysin, neurofilament, and focally positive for S-100 protein and they stain negative for desmin, actin, leukocyte common antigen, cytokeratin, and the Ewing antigen[6]. Urinary catecholamines are raised in >90% of neuroblastomas but only in 33% of perinatal neuroblastomas. I^{131} or I^{123} (preferred) meta-iodo benzyl guanidine (MIBG) scintigraphy is highly sensitive and specific. The treatment of neuroblastoma depends on the stage, and it includes surgical excision, multiagent chemotherapy, and bone marrow transplantation[7].

Key words: Congenital Neuroblastoma; Pneumonia; Round Cell Tumors

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