Severe Pulmonary Arteriopathy in a Neonate with Congenital Rubella Syndrome and Patent Ductus Arteriosus

SUPREET KHURANA[1], AKRITI BANSAL[2], SHIV SAJAN SAINI[1], ANAND MISHRA[3] AND PRAVEEN KUMAR[1]

From [1]Division of Neonatology, Department of Pediatrics; [2]Department of Pathology; and [3]Department of Cardiothoracic Vascular Surgery; Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Correspondence to: Dr Shiv Sajan Saini, Assistant Professor, Division of Neonatology, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh, India. sajansaini1@gmail.com

Neonates with congenital rubella syndrome (CRS) are known to have associated congenital cardiac malformations. Patent ductus arteriosus (PDA) is one the most common cardiac anomalies associated with CRS. PDA refractory to medical management and associated with ventilatory dependence is considered for surgical ligation. However, the management of PDA can be challenging in the presence of underlying lung disease or pulmonary vascular disease. Outcomes after closure in neonates are dependent upon age, weight, nutritional status, pre-operative pulmonary arterial hypertension and presence of chronic lung disease. We present a neonate with CRS who required surgical PDA closure. The neonate developed severe pulmonary arterial hypertension which led to fatal outcome. The clinical course is corroborated with histo-pathological changes observed on the autopsy of this neonate.

Keywords: *Complications, Epidemiology, German measles, Pregnancy.*

CLINICAL PROTOCOL

History and examination: A male neonate was born at 35 weeks gestation with a birth weight of 1016g to a primigravida mother with the antenatal history of oligohydramnios and intra-uterine growth retardation (IUGR). The baby was delivered by induced vaginal delivery secondary to meconium stained amniotic fluid. His APGAR scores were 6 and 8 at 1 and 5 minutes after birth. His physical examination revealed symmetrical (IUGR) [head circumference 25 cm (4.5 z-score), Ponderal index= 2], bilateral cataract and hepatosplenomegaly.

Investigations: His complete hemogram revealed thrombocytopenia; cranial ultrasonography (USG) was suggestive of increased echogenicity in bilateral basal ganglia and periventricular region, and USG abdomen was normal. Two-dimensional echocardiography (2D-ECHO) was suggestive of atrial septal defect (ASD) and 4 mm patent ductus arteriosus (PDA) with left to right shunt. Toxoplasma, rubella, cytomegalovirus (CMV) and herpes (TORCH) work-up revealed positive Rubella Immunoglobulin M (IgM). His renal and liver function tests were normal. His acute phase reactants were negative and blood/ cerebrospinal fluid (CSF) cultures were sterile.

Course and management: The baby was managed as a case of congenital rubella syndrome. He developed tachypnea after birth requiring oxygen delivered *via* nasal prongs oxygen for initial 2 days. His enteral feeds were slowly hiked and he reached full enteral feeds on 6th day. He again developed respiratory distress on day 11 requiring re-initiation of head box oxygen. His chest radiograph revealed inhomogeneous infiltrates. Antibiotics were initiated and were stopped after 5 days as his septic workup was negative and his blood cultures were sterile. However, he continued to require oxygen by nasal prongs. On day 18, he developed clinical signs of congestive heart failure (CCF) requiring invasive ventilation, fluid restriction, and intravenous furosemide. He also received red blood cell transfusion as he had high inspired oxygen requirement. His chest *X*-ray was suggestive of consolidation and intravenous antibiotics were restarted. High frequency ventilation was started in view of worsening respiratory distress. His respiratory status improved and he was shifted to synchronized intermittent mandatory ventilation (SIMV). His blood and CSF cultures were unremarkable and antibiotics were stopped after 7 days. Within the next 48 hours, the CCF worsened requiring initiation of dobutamine infusion and digoxin. Digoxin was later withheld as he developed signs of digoxin toxicity. As his CCF was resistant to medical management, PDA ligation was planned.

Pre-operative echocardiography showed large PDA with moderate pulmonary arterial hypertension (PAH); pulmonary arterial pressures were 45 mm Hg with Qp:Qs (Pulmonary : Systemic blood flow) = 2:1. On day 48 of life, he underwent bed-side PDA closure surgery in the NICU, during which 5 mm PDA was closed with a

titanium clip. The aortic arch was intact. Chest was closed with left pleural drain *in-situ*. After 2 hours, his ventilatory requirement increased. Echocardiography revealed closed PDA, moderate to severe PAH with poor cardiac contractility (ejection fraction 30%). The baby was initiated on dobutamine and milrinone infusions as inhaled nitric oxide was unavailable at that time. However, pulmonary pressures did not improve requiring initiation of sildenafil. Nevertheless, the baby gradually developed respiratory failure, refractory shock and expired on day 58 of life. His blood cultures obtained before death were sterile.

Clinical analysis: In view of clinical findings and examination–preterm symmetric IUGR neonate, microcephaly, cataract, PDA–along with laboratory investigations showing thrombocytopenia and rubella IgM sero-positivity, diagnosis of laboratory confirmed congenital rubella syndrome (CRS) was made in accordance with WHO CRS Surveillance standards [1]. The neonate had CCF, which was refractory to medical management. He also had underlying BPD contributed by prematurity, PDA, intercurrent infections and chronic ventilator dependence. The underlying reason for his postoperative deterioration was refractory CCF and PAH. Other possible differentials included healthcare associated bacterial infections (HAI), and acquired CMV infection. HAI were ruled out by blood cultures and sepsis workup. Acquired CMV (through blood transfusions or perinatally acquired) was ruled out by DNA PCR as well as negative serology. The sensitivity and specificity of reverse transcriptase polymerase chain reaction as per literature varies between 83-95% and 95-100% respectively [2].

The reason for deterioration in the post-operative period seemed to be pulmonary arterial hypertension. It was secondary to either broncho-pulmonary dysplasia (BPD) or/and worsening due to surgery induced inflammation [3]. It is evident from the literature that a long-standing large sized PDA can damage pulmonary parenchyma and cause re-modeling of pulmonary vasculature, which possibly happened in our case [4]**.** Preoperative hemodynamic information does not correlate well with post-operative outcome for various reasons [4].

Open-house Discussion

Treating unit senior resident: The case was challenging in terms of managing ventilation and medically refractory CCF which in presence of a large PDA required surgical closure of PDA. But on the hindsight closure actually worsened the preexistent pulmonary hypertension. In the autopsy of lungs, we expect findings concomitant with bronchopulmonary dysplasia and distortion of normal lung architecture in form of alveolar simplification, smooth muscular hyperplasia, peribronchiolar and interstitial fibrosis, areas of atelectasis and abnormal microvasculature. Also we have suspicion of CMV pneumonitis. The findings of CNS will be important due to USG head abnormalities in neonate. Whether some of findings in heart are missed will also be informative.

Cardiologist: Post PDA ligation syndrome is unlikely to lead to worse outcome in this neonate as it was well managed and cardiac functions improved echo-cardiographically after starting dobutamine. Pulmonary hypertension crisis is known in cases with only severe pulmonary vasoconstrictive disease and is less likely to be a cause of mortality as in an unpublished study of 500 neonates with moderate to large PDA, wherein cardiac functions improved after PDA ligation, mortality was decreased post operatively.

Treating unit consultant: Post PDA ligation syndrome does not seem to be a contributor of mortality in our neonate. We expect BPD changes in lungs that seem to be contributed by multiple intercurrent illnesses and by a large PDA. Also we failed to identify any infectious illness by means of cultures. Although we tried to exclude congenital CMV by means of investigations, but perinatally acquired CMV remains a possibility.

Pediatrician 1: Congenital Rubella syndrome can have findings of bilateral basal ganglia calcifications, peri-ventricular leucoencephalopathy and temporal cysts on brain.

Pediatrician 2: Chest x-rays were suggestive of hyperinflation in the patient, which due to increased lung volumes can worsen pulmonary hypertension.

Treating unit senior resident: Our patient was judiciously managed with high frequency ventilation and required high MAP and fraction of inspired oxygen (FiO_2). We could not decrease the ventilatory pressures as there was severe parenchymal disease with co-existing PAH.

PATHOLOGY PROTOCOL

A complete autopsy was performed. Weight of neonate was 1438 gm, crown heel length was 40 cm and occipitofrontal circumference (OFC) were 27 cm, All these parameters were below -2 z-score for age. There was 10 mL serous fluid in pericardial cavity. The weight of heart was 20 g with globular shape and blunt apex and situs solitus. The pulmonary trunk was grossly dilated. PDA was clipped and an ASD measuring 5 mm was identified. Right ventricular wall was hypertrophic and measured 5 mm (normal values 1.3-4 mm) [5]. Microscopy of the right

ventricle revealed mild anisonucleosis of the cardiac muscles indicating right ventricular hypertrophy.

Both lungs weighed together 90 and were overweight. The pleurae were dull and fibrins tags were noted on lungs suggestive of pleuritis. Both the lungs showed areas of consolidation and hemorrhage. Microscopy showed areas of intra-alveolar hemorrhage and interstitial widening with no evidence of fibrosis. Interstitial widening was predominantly caused by pulmonary capillary proliferation. In addition, there was abundance of type 2 pneumocytes in alveoli. Reticulin stain demonstrated interstitial widening with pulmonary capillary proliferation. There was evidence of pulmonary arterial hypertension in the form of pulmonary arteriopathy. The pre-acinar and intra-acinar pulmonary arteries showed intimal hyperplasia with medial hypertrophy and adventitial thickening. A few arteries had complete occlusion of lumen due to intimal proliferation. These changes were better appreciated on elastic von- Gieson stain (***Web Fig.* 1**). There was an area of consolidation with neutrophilic inflammatory infiltrate in bronchial lumen and surrounding alveoli confirming bronchopneumonia (***Fig.* 2**). Stains for gram positive, gram negative bacteria and PAS stains for fungus were negative. No CMV inclusions were found.

Brain weighed 320 g and OFC was 27 cm suggestive of microcephaly. There was softening of white matter and focal calcifications in the white matter, periventricular and basal ganglia region (***Web Fig.* 2**). Micronodules were appreciated in white matter and basal ganglia. Edema and pallor was found in periventricular area consistent with periventricular leucomalacia (***Web Fig.* 3**).

Liver, spleen, kidney, urinary systems, esophagus, stomach. thymus, bone marrow, lymph nodes, adrenal and testes were normal.

Final autopsy diagnosis:

A 2-month old male with evidence of congenital rubella syndrome and surgically clipped PDA:

- Pulmonary artery hypertension - Pulmonary arteriopathy grade 3, pulmonary micro vasculopathy
- Bronchopneumonia
- Congenital heart disease- ASD, PDA
- Microcephaly, periventricular leukomalacia, calcifications in brain

Open-house Discussion

Pediatrician 3: Congenital rubella syndrome surveillance is being conducted in 5 centers since 2016 (Postgraduate Institute of Medical Education and Research, Chandigarh; All India Institute of Medical Sciences, Jodhpur; KEM Hospital,Pune; Indira Gandhi Institute for Child Health, Bengaluru; Christian Medical College, Vellore). In a period of 8 months, during December 2016-July 2017; 207 cases of CRS were identified as clinical cases with 72 laboratory confirmed cases (35% positivity rate). Among laboratory confirmed cases of CRS, 83% had congenital heart diseases, 62% had eye manifestations and 35% had hearing deficits on 1-year follow up. Most common associated condition is congenital heart disease, though cataract had been most common defect leading to suspicion of CRS. Sixty percent mothers, whose neonates developed CRS, were <26 years at age of conception [6].

Treating unit consultant: Pathological findings were quite interesting. As opposed to our expectations of significant fibrotic changes in lungs affected with BPD, there were predominant angio-dysplastic changes. At 35 weeks of gestation, as lungs are in saccular phase of development, exposure to risk factors leading to chronic lung disease (CLD) can predispose to development of capillary proliferation rather than fibrosis. Findings of calcifications in central nervous system were also of interest as toxoplasma and CMV are common congenital infections known to cause these findings rather than CRS.

DISCUSSION

The burden of congenital rubella in developing nations is much higher than developed countries, where annual incidence of congenital rubella is less than one per hundred thousand live births [7]. As per the latest WHO update, there has been a constant increase in number of cases of CRS over the last decade [8]. An infant with CRS can present with one or more of the following clinical features – cataract, congenital glaucoma, congenital heart disease (PDA or peripheral pulmonary stenosis), hearing impairment, hepatosplenomegaly, microcephaly, meningoencephalitis, radiolucent bone disease etc [9]. The clinical presentation of neonates with CRS depend on the gestational age of fetus at the time of maternal infection. Structural heart defects and eye abnormalities occur if maternal infection is acquired before eight weeks; while hearing defects are more common, if infections occurs till 18 weeks of pregnancy [10]. Maternal infection later in course of pregnancy might manifest with only intrauterine fetal growth restriction. The index neonate manifested with several clinical features suggestive of CRS and the diagnosis was also confirmed with presence of rubella specific IgM antibodies. In addition to the several common features of

CRS, the index neonate also had calcifications in white matter, periventricular area and basal ganglia [11]. The most common finding in CRS patients is that of microcephaly as in our case and most consistent pathological findings are that of vascular destruction [12]. Intracranial calcifications are more frequently associated with congenital CMV and toxoplasmosis but are rarely reported in CRS [13].

There is no definitive management of CRS. The treatment is primarily symptomatic, based on organ system involvement [14]. Due to multiple organ involvement, a multidisciplinary team involvement is warranted [15]. The management of PDA was tricky in our case. PDA closure was warranted as the PDA size was big, CCF was not fully controlled with medical therapy and ventilator dependence [16]. However presence of concomitant pulmonary arterial hypertension and underlying BPD posed significant challenge for deciding surgical closure. Although PDA closure is contraindicated in severe pulmonary artery disease, it can be considered in the presence of reversible pulmonary disease [17]. PDA closure in neonates with PAH is recommended in cases with lower baseline pulmonary vascular resistance along with lower pulmonary arterial pressures, Qp:Qs ratio of >1.5, and a pulmonary arterial to systemic arterial pressure ratio <0.5 [18,19]. In this case, Qp: Qs ratio was 2:1 and pulmonary arterial pressure was 45 mm Hg (moderately elevated) prior to PDA ligation. Thus, after excluding irreversible pulmonary vascular disease, the surgical ligation was decided in multidisciplinary meeting.

The baby had persistent ventilator requirement after PDA closure, which worsened and eventually baby died of respiratory failure. BPD development is associated with the altered pro-inflammatory cytokines/chemokines profile as well as mediators of parenchymal and vascular remodeling. Waleh and colleagues reported that the surgical PDA closure led to increase in the expression of pro-inflammatory mediators (COX-2, TNF-alpha, and cells expressing CD14), and decreased expression of angiogenesis genes (angiopoietin-2 and TGF beta 3) [20]. Additionally, surgical PDA ligation decreased pulmonary alpha-ENaC containing channels expression, which is involved in trans-epithelial sodium transport related to clearance of alveolar fluid. Furthermore, these changes were observed in lung tissue taken from the side opposite to the ligation even after one week of surgery. Thus, in our case possibly the surgical ligation has escalated the underlying pro-inflammatory state which was already present due to BPD. The autopsy findings are also suggestive of the same. The histopathology of baby's lung showed the areas of consolidation with neutrophilic inflammatory infiltrate without any evidence of bacteria, fungus or CMV. These findings clearly point towards a non-infectious pro-inflammatory state. It is also noteworthy that ante-mortem sepsis workup was negative. Similar observations have previously been reported by other authors [21]. These findings have clear implications in the clinical practice. The physicians should be aware of this phenomenon. All possible efforts should be done to provide gentler ventilation, improved nutrition to counter pro-inflammatory states in such setting. There is definite role of multidisciplinary meetings including neonatology, cardiology and cardiothoracic surgery to take decision in case to case basis considering physiology of these neonates. Further research is needed to optimize the timings of surgical ligation in such complex settings.

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Discussants: *Clinical discussant pediatrician*: Akhil Raj MS, *Treating unit senior resident*: Supreet Khurana; *Cardiologist*: Ashish Tiwari; *Treating unit consultant*: Shiv Sajan Saini; *Pediatrician* 1: Sumeet Dhawan; *Pediatrician* 2: Suresh Kumar Angurana; *Pediatrician 3*: Sanjay Verma, *Clinical discussant pathologist*: Akriti Bansal.

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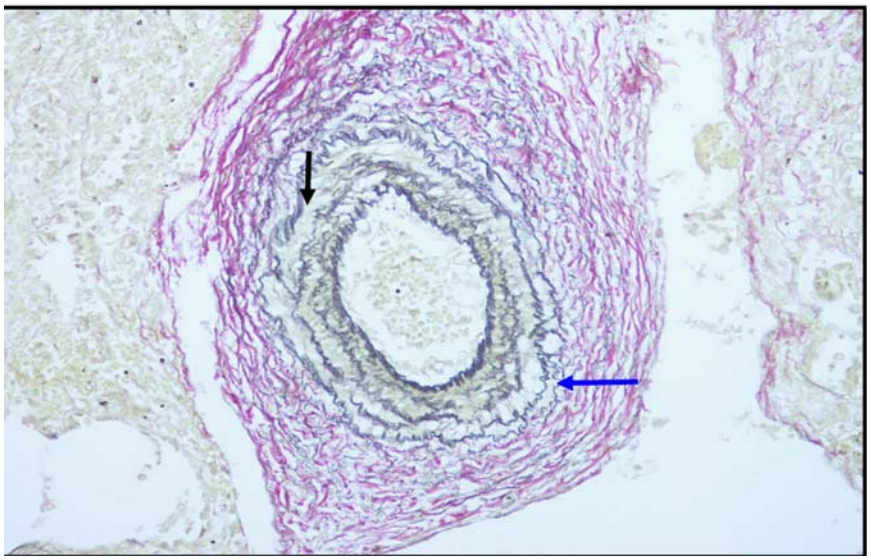
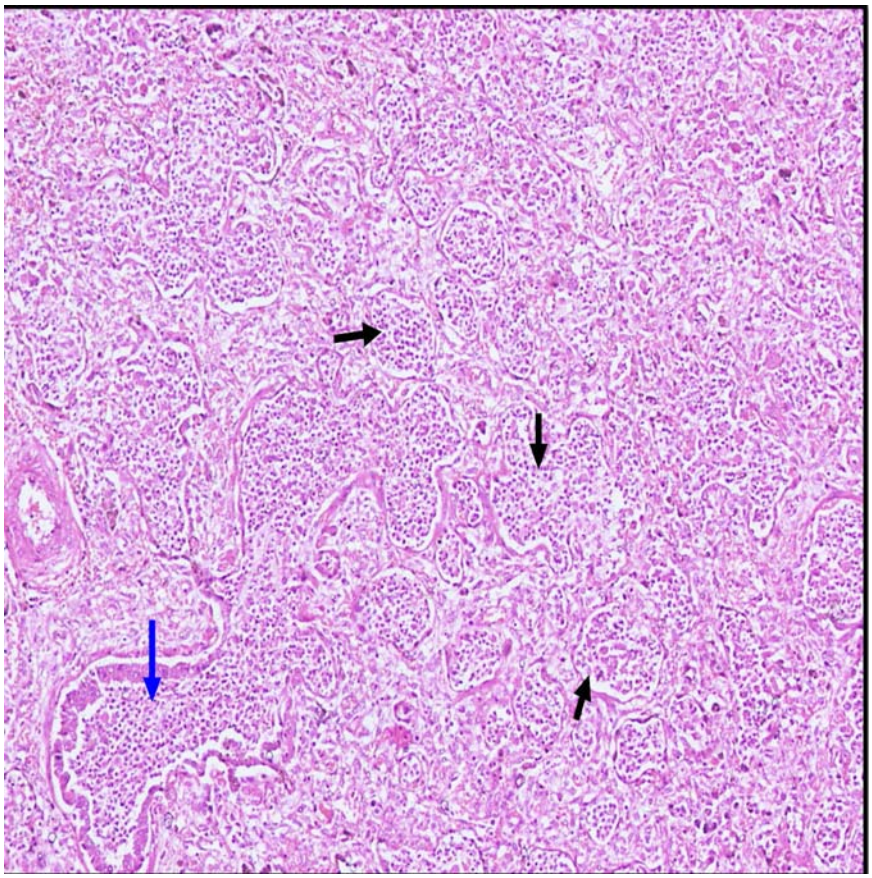
REFERENCES

1. World Health Organization ;WHO 2014.WHO-recommended Surveillance Standard of Rubella and Congenital Rubella Syndrome: Available from *http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/rubella_standards/en.* Accessed December 11, 2017.
2. Mace M, Cointe D, Six Caroline, Levy-Bruhl D, Chatelet IP, Ingrand D, *et al*. Diagnostic value of Reverse Transcription- PCR of amniotic fluid for prenatal diagnosis of congenital rubella infection in pregnant women with confirmed primary rubella infection. J Clin Microbiol. 2004;42:4818-20.
3. Niu MC, Mallory GB, Justino H, Ruiz FE, Petit CJ. Treatment of severe pulmonary hypertension in the setting of the large patent ductus arteriosus. Pediatrics. 2013;131:e1643-49.
4. Bhalgat PS, Pinto R, Dalvi VB. Transcatheter closure of large patent ductus arteriosus with severe pulmonary

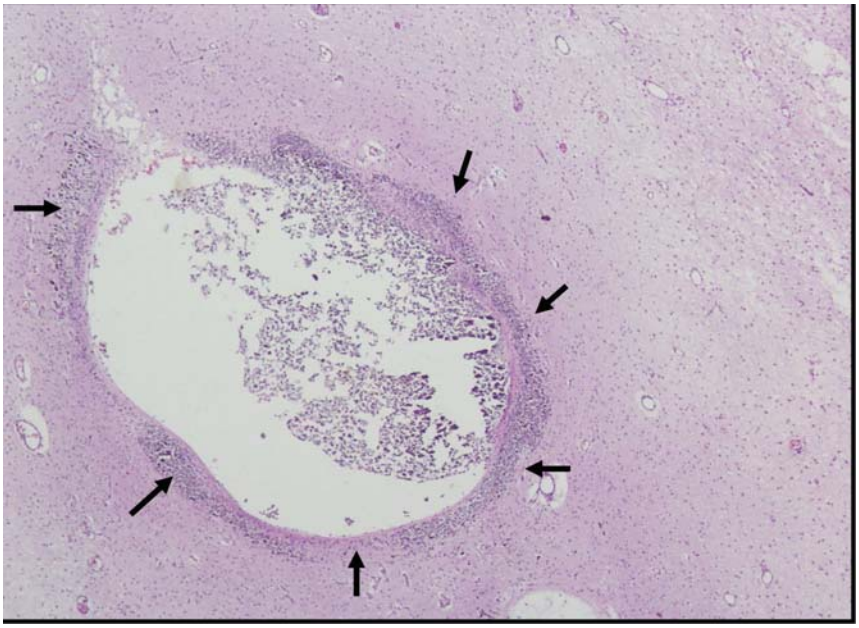
arterial hypertension: Short and intermediate term results. Ann Pediatr Cardiol. 2012;5:135-40.
5. Guzeltas A, Eroglu GA. Reference values for echocardiographic measurements of healthy newborns. Cardiol Young. 2012;22:152-7.
6. Murhekar M, Bavdekar A, Benakappa A, Santhanam S, Singh K, Verma S, *et al*. Sentinel surveillance for congenital rubella syndrome- India, 2016-17. MMWMR Morb Mortal Wkly Rep. 2018;67:1012-6.
7. Singh MM. Need for rubella vaccination in India. BMJ .2014;349:g4844.
8. World Health Organization. WHO 2018. Global and Regional Immunization Profile South-East Asia Region. Available from: *http://www.who.int/immunization/monitoring_surveillance/data/gs_searprofile.pdf*. Accessed November 3, 2018.
9. Lanzieri T, Redd S, Abernathy E, Icenogle J. Congenital Rubella Syndrome. Centers for Disease Control and Prevention 2018. Available from: *https://www.cdc.gov/vaccines/pubs/surv-manual/chpt15-crs.html.* Accessed December 12, 2018
10. Dobson RS, Edwards SM, Weisman LE, Armsby C. Uptodate 2018. Congenital Rubella Syndrome: Clinical Features and Diagnosis. Available from: *https://www.uptodate.com/contents/congenital-rubella-syndrome-clinical-features-and-diagnosis.* Accessed December 12, 2018.
11. Rao JN, Chancham S, Reddy UN, Nagasravani J, Mazher N, Mustafa ST. Congenital rubella syndrome with basal ganglia calcification and bilateral nuclear cataracts in a neonate: A rare entity. Sch J Med Case Rep. 2014;2:470-2.
12. Eckstein M, Vijayalakshmi P, Killedar M, Gilbert C, Foster A. Etiology of childhood cataract in south India. Br J Ophthalmol. 1996;80:628-32.
13. Numazaki K, Fujikawa T. Intracranial Calcifications with congenital rubella syndrome in a mother with serological immunity. J Child Neurol. 2003;18:296-7.
14. Cherry JD, Adachi K. Rubella virus. *In*: Cherry JD, Harrison GJ, Kaplan SL, editors. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed, Philadelphia: Elsevier Saunders, 2014. *P*. 2195.
15. Plotkin SA, Reef SE, Cooper L S Alford CA. Rubella. *In*: Remington, JS, Klein, JO, Wilson, CB, editors, Infectious Diseases of the Fetus and Newborn Infant, 7th ed, Philadelphia: Elsevier Saunders, 2011. *P*. 861.
16. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, *et al.* Management of patent ductus arteriosus. Circulation. 2008;118:e714.
17. Rigby ML. Closure of a large patent ductus arteriosus in adults: first do no harm. Heart. 2007;93:417.
18. Zhang DZ, Zhu XY, Lv B, Cui CS, Han XM, Sheng XT, *et al*. Trial occlusion to assess the risk of persistent pulmonary arterial hypertension after closure of a large patent ductus arteriosus in adolescents and adults with elevated pulmonary artery pressure. Circ Cardiovasc Interv. 2014;7:473-81.
19. Yan C, Zhao S, Jiang S, Xu Z, Huang L, Zheng H, *et al*. Transcatheter closure of patent ductus arteriosus with severe pulmonary arterial hypertension in adults. Heart. 2007;93:514-8.
20. Waleh N, Mccurnin CD, Yoder AB, Shaul PW, Clyman RI. Patent ductus arteriosus ligation alters pulmonary gene expression in preterm baboons. Pediatr Res. 2011;69:212-6.
21. Niu MC, Mallory GB, Justino H, Ruiz FE, Petit CJ. Treatment of severe pulmonary hypertension in the setting of the large patent ductus arteriosus. Pediatrics 2013;131:e1643-49.



***Web Fig.* 1** *Photomicrograph from intra-acinar pulmonary artery showing intimal thickening, reduplication of internal elastic lamina and adventitial thickening (Elastic von Gieson ×400).*



***Web Fig.* 2** *Photomicrograph from focus of bronchopneumonia showing polymorphs and lymphocytes in bronchiole and adjacent alveolar spaces (H&E×100).*



***Web Fig.* 3** *Photomicrograph showing focal areas of calcification in perivascular spaces of white matter (H&E ×100).*