Journal of Intensive and Critical Care
ISSN:2471-8505

Open access Case Report

Successful Combination Therapy for Pulmonary Hypertension in Incontinentia Pigmenti: Case Report and Review of the Literature

Mattia Zanin[1*], Enrico Bonaveglio[1], Martina Scanu[1], Annalisa Longobardo[1], Stefania Iannandrea[1], Elisa Catalano[1], Fortunato Ciliberto F[1], Sergio Grassitelli[1], Francesca Fusco[2], Mirela Bojan[3], Simona Quaglia[1]

[1]*Department of Anesthesiology, Regina Margherita Hospital, Torino, Italy*
[2]*Department of Genetics and Biophysics, Adriano Buzzati-Traverso, IGB-CNR, Naples, Italy*
[3]*Department of Congenital Cardiac Unit, Marie Lannelongue Hospital, Le Plessis Robinson, France*

ABSTRACT

Pulmonary Arterial Hypertension (PAH) is a well-known but very rare and severe complication of Incontinentia Pigmenti (IP). Only few cases are reported in literature, most of them fatal. Recently, some reports described better outcome with a more aggressive treatment combining multiple pulmonary vasodilators and immunomodulatory drugs.

We present the case of a three months old female diagnosed with IP and severe PAH refractory to inhaled nitric oxyde, admitted in cardio-pediatric ICU for mixed cardiogenic and hemorrhagic shock and treated with a combination of high dose iNO, sildenafil, iloprost, TNF-alpha inhibitor and steroids. Following this treatment, PAP dropped from iso-systemic to half systemic, and PVRI halved as well. After an episode of septic shock and a hospital acquired pneumopathy from Pneumocystis jirovecii, the baby was discharged home in good conditions at the age of six months.

Keywords: Pulmonary hypertension; Incontinentia pigmenti; Pediatric intensive care unit

ABBREVIATIONS

(BAL) bronchoalveolar lavage; CADASIL Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; (iNO) inhaled nitric oxide; (IP) Incontinentia Pigmenti; (IUGR) intra-uterine growth restriction; (PAP) pulmonary artery pressure; (PAH) pulmonary arterial hypertension; (PICU) pediatric intensive care unit; (PFO) patent foramen ovale; (PPHN) persistent pulmonary hypertension of the neonate; (PRBC) packed red blood cells; (RHC) right heart catheterization; (RA) right atrium; (RV) right ventricle; (NIV) non-invasive ventilation; (HFNC) high flow nasal cannula; (IV) intra-venous; (sc) subcutaneous; (aer) aerosol.

INTRODUCTION

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome, OMIM 308300) is a rare X-linked dominant genodermatosis due to mutations in IKBKG/NEMO gene, leading to a loss or a reduction of NF-κB activation, a crucial transcription factor involved in inflammation and apoptosis [1]. Orphanet recently estimated a birth prevalence of 1.2/100.000 for IP in Europe [2]. Affected males usually die in utero, while females always survive due to X chromosome lyonization. Clinical features are variable and mostly concern skin, eye, teeth and CNS. The skin lesions usually follow lines of Blaschko, and are classified into four stages (I vesicobullous; II verrucous/hyperkeratotic; III hyper-pigment-

Received:	30-Aug-2022	**Manuscript No:**	IPJICC-22-14197
Editor assigned:	01-Sep-2022	**PreQC No:**	IPJICC-22-14197 (PQ)
Reviewed:	15-Sep-2022	**QC No:**	IPJICC-22-14197
Revised:	20-Sep-2022	**Manuscript No:**	IPJICC-22-14197 (R)
Published:	27-Sep-2022	**DOI:**	10.35248/2471-8505-8.9.100

Corresponding author Mattia Zanin, Department of Anesthesiology, Regina Margherita Hospital, Torino, Italy, Tel: +39 011 3135601; E-mail: mzanin@cittadellasalute.to.it

Citation Mattia Zanin, Enrico Bonaveglio, Martina Scanu, Annalisa Longobardo, Stefania Iannandrea, et al. (2022) Successful Combination Therapy for Pulmonary Hypertension in Incontinentia Pigmenti: Case Report and Review of the Literature. J Intensive Crit Care. 8(9):100.

ed; IV atrophic/hypopigmented); they are often the first clinical manifestation in the neonatal period [3-5].

IP can be associated with cardio-pulmonary anomalies [6] both anatomical [7,8] and functional. Among these, Pulmonary Arterial Hypertension (PAH) is an uncommon complication of IP. In most cases, PAH associated with IP is refractory and fatal [9-11]. Recently, some authors reported better outcomes with new therapeutic approaches, such as tadalafil [12] or combination therapies with multiple anti-PAH drugs [4] and immunomodulation [6,13].

CASE PRESENTATION

A Caucasian female was born in a peripheral Hospital at 38th week of gestational age from caesarian section for IUGR and abnormal cardiotocography. Neonatal weight was 2070 g. She had a good post-natal adaptation. Vesicular hyperchromic cutaneous lesions were noted at birth. Clinical diagnosis of IP was made at the age of 8 weeks. A trans-thoracic echocardiography performed during the diagnostic work up showed dilated RV, LV D-shape, PFO with bidirectional shunt and moderate to severe tricuspid regurgitation with ΔRV/RA=80 mmHg. PH was suspected and the baby was sent to our center for further investigations.

At the age of 12 weeks, a RHC was performed under general anesthesia and showed severe pulmonary hypertension with a nearly iso-systemic pulmonary pressure (PAP=66/23 (43) mmHg) and PVRI=9, 54 WU/m^2 refractory to vasodilation test with FiO_2 100% and iNO=20 ppm. No anatomic abnormalities were noted, leading to diagnosis of PAH. No complications occurred, the patient was extubated and sent to general ward.

Few hours later, the baby was transferred to Cardiac-PICU with severe mixed shock from both bleeding from venous cannula and acute right ventricular failure. She was intubated and started on mechanical ventilation with FiO_2=100%, she received a PRBC transfusion and was started on inotropic support (adrenaline 0.05 mcg/kg/min+ milrinone 0.5 mcg/kg/min). Following a multidisciplinary evaluation, an aggressive multi-drug therapy was introduced, combining anti-PAH (high dose iNO, sildenafil, bosentan and iloprost) and immunomodulatory treatment (etanercept and steroids, following immunologic specialistic evaluation), according to **Table 1** and **Figure 1** shown below. The patient also received prophylactic heparin.

Table 1: Posology schedule for anti-PAH and immunomodulatory therapies. Please note PICU day 17 as the onset of alveolar bleeding and septic shock.

PICU day	Mech- ventilation / iNO	Sildenafil (enteral)	Bosentan (enteral)	iloprost (IV)	iloprost (aerosol)	Steroid	Etanercept
1	Intubation / 40 ppm	Start 3.5 mg q8h os					
2	Intubation / 40 ppm	Start 3.5 mg q8h os		Start 0.2 ng/kg/min iv		start methylprednisolone 3.5 mg q12h iv	Start 3 mg/ week sc (I dose)
3	Intubation / 40 ppm	Start 3.5 mg q8h os	Start 3 mg q12h os	Augment + 0.1-0.15 ng/kg/min q6h			
4	20 ppm	3.5 mg q6h					
7	weaning, stop			2 ng/kg/min (steady-state dosage)			
9	extubation start NIV / HFNC						3 mg/week (II dose)
12				De-escalation	Start 1 mcg q4h	de-escalation	
13					1.5 mcg q4h		
15				stop			
16						Stop methylprednisolone	3 mg/week (III dose)
17	Intubation / 40 ppm	stop	stop		stop	Start hydrocortisone 6 mg q6h iv	
19						+ Ig ev 1.5 g/12h	
20	30 ppm	Start 3.5 mg q6h	Start 3 mg q12h				
23	10 ppm						Not done
24	stop						

28				Stop hydrocortisone	
30	extubation	prosecute	prosecute		Not done

(PICU) pediatric intensive care unit; (iNO) inhaled nitric oxide; (NIV) non-invasive ventilation; (HFNC) high flow nasal cannula; (IV) intra-venous; (sc) subcutaneous

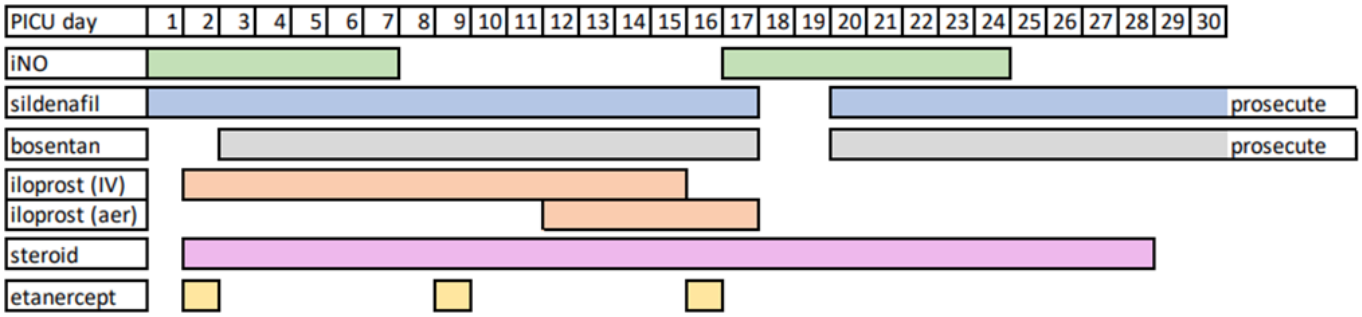

Figure 1: Timing for anti-PAH and immunomodulatory therapies. Please note PICU day 17 as the onset of alveolar bleeding and septic shock.

The improvement in cardiac function led to extubation on day 9. Unfortunately, the patient was re-intubated because of a life threatening respiratory failure and septic shock due to an alveolar hemorrhage and hospital acquired pneumonia. The patient showed thrombocytopenia, considered to be a complication of the treatments in progress. Therefore, iloprost and etanercept were suspended. The only significant microbiologic finding was a Pneumocystis jirovecii identified in a BAL collected more than one week later. The wide spectrum antibiotic therapy started initially was down escalated to Cotrimoxazole. A subsequent thoracic CT scan revealed bilateral consolidations and diffused ground glass opacities. For reference, since it was March 2020 in North Italy, BAL for SARS-CoV2 resulted negative.

The baby was successfully extubated on day 30, she was transferred to the general ward and then to a spoke hospital one month later. She was finally discharged at home at the age of 6 months. At discharge, trans-thoracic echocardiography showed hypertrophic and less dilated RV, no LV D-shape, mild tricuspid regurgitation (ΔRV/RA=30 mmHg) and minimal left to right shunt through the PFO. Bosentan and sildenafil were prosecuted home.

Moreover, at discharge the baby presented a mild neurodevelopmental delay, mostly attributable to the long hospitalization and the necessary use of sedative drugs. No eyes and fundus abnormalities were found during the entire hospitalization, but it was not possible to schedule second level exams (i.e. retinography). A brain MRI performed at the age of 7 months was normal.

Follow up RHCs executed at the age of 7 and 15 months showed PAP=1/3 of systemic pressure; PVRI were respectively 4, 45 WU/m^2 and 2, 18 WU/m^2, therefore Sildenafil was interrupted with no complications. Succeeding follow up echocardiography at 2 years from the episode showed a normalized RV, no LV D-shape and minimal tricuspid valve regurgitation, thus also Bosentan was discontinued. At this age, the baby weighted 11 kg and reached the principal neurodevelopmental cornerstones for her age.

According to Fusco F the results of genetic testing done during the hospitalization turned up positive for the common de novo exon 4–10 deletion (IKBKGdel) in IKBKG/NEMO gene and the diagnosis was confirmed by genetic medicine specialist.

The parents of the baby gave informed consent for the description of this case.

DISCUSSION

Here we report the case of a patient with IP and severe PAH who survived the neonatal period. To the best of our knowledge, the case reports cited below are the only reports of a good outcome in patients diagnosed with IP and PAH, after exclusion of the ones where pulmonary hypertension was due to congenital anatomical heart defect [7,8].

Onnis [6] and Mizuno [12] reported good outcomes in two neonates with IP and PAH partially responsive to iNO: the first received bosentan and sildenafil, the second received tadalafil. None received steroids or immunomodulatory drugs. However, because both were neonates and became symptomatic in the very first days of life, when the pulmonary vascular resistances are still high, a possible overlap with PPHN, which is often transitory, has to be considered.

On the other hand, the patient described by Atallah [13] was very similar to our patient: she developed severe refractory PAH at the age of 4 months when she became critically ill and she had a favorable outcome after being started on a combination of aggressive anti-PAH therapy and immunomodulation with etanercept and steroids.

There are few data about the mechanisms involved in the pathogenesis of IP-associated PAH. In IP, the deficiency of IKKgamma/NEMO protein leads to a loss of NF-κB activation pathway, making the cell more susceptible to cytokines induced apoptosis, particularly TNF-alpha [15]. This is supposed in the endothelial cells of retinal and nervous tissues [16]. Additionally, reduced brain perfusion due to capillary loss was reported in selectively deleting Nemo brain endothelial cells in mouse model [17]. These findings suggest a microangiopathic origin of CNS lesions which could be assimilated to a “small-vessel disease”, such as CADASIL [18]. A phlogistic microangiopathic pathogenesis for IP-associated PAH is possible too. Furthermore, involvement of

NF-κB pathway has been described in the pathogenesis of induced PAH in rats [19-21]; however its role in IP-associated PAH remains unclear. These considerations suggest the usefulness of etanercept and steroids in this setting. Further studies are needed to investigate the molecular pathogenesis of PAH in IP.

In our patient, etanercept and iloprost were suspended after three weeks concomitant with the onset of septic shock and alveolar hemorrhage. Reduced platelets adhesion and increased coagulation time are well-known side effects of iloprost; besides, iloprost-induced thrombocytopenia was reported as well [22].

Etanercept is a monoclonal antibody inhibitor of TNF-alpha. Thrombocytopenia and opportunistic infections are among its main side effects. No infectious agent was initially identified at the onset of sepsis in our patient, and Pneumocystis jiroveci was found in BAL more than one week later. It is therefore not possible to speculate whether sepsis was related to this pathogen or not. However, previous authors reported associations between the use of anti-TNF-alpha and Pneumocystis jiroveci pneumonia, both in adults [23] and in children [24].

CONCLUSION

PAH is a rare but potentially fatal finding in IP. To date, the literature suggests that IP is associated with a microangiopathic phlogistic origin in CNS lesions, due to increased cytokine-induced endothelial apoptosis (mainly TNF-alpha). It is not known whether PAH is a result of a similar pathophysiological process at the level of the pulmonary vessels. Combination therapy with both multiple pulmonary vasodilators and immunomodulatory drugs may be effective in treating this pulmonary complication in IP. Considering drug interactions, close monitoring for adverse effects is suggested.

ACKNOWLEDGEMENT

We would like to thank all the healthcare professionals involved in the care of this little child, principally nurses, intensive care doctors and cardiologists from the Pediatric Cardiac Intensive Care Unit in Regina Margherita Hospital, Turin, Italy.

A special thanks to the medical consultants constantly engaged in the management of this case, in particular Dr F. Licciardi (Immuno-rheumatology Unit, Regina Margherita Hospital) and Dr C. Scolfaro (Infectious Diseases Unit, Regina Margherita Hospital), Professor A. Mussa (Pediatric Genetic Unit, Regina Margherita Hospital) and Dr. Simona Quaglia (Chief of Pediatric Anesthesia and PICU Service, Regina Margherita Hospital, Turin)

CONFLICT OF INTEREST

The authors have indicated they have no conflicts of interest relevant to this article to disclose.

FUNDING

The authors received no financial support for the research and publication of this article.

ARTICLE SUMMARY

Pulmonary hypertension associated with Incontinentia Pigmenti may be treated by aggressive combination therapy.

Specific Contributor's Statement Page

Dr Zanin conceptualized the project, examined the literature, drafted the initial manuscript, reviewed and revised the manuscript.

Dr Grassitelli (chief of Pediatric Cardiac ICU, Regina Margherita Hospital, Turin) and Dr Bonaveglio coordinated and supervised the project, promoted the acquisition of data, evaluated and revised the final manuscript.

Dr Scanu, Dr Longobardo, Dr Iannandrea, Dr Catalano, Dr Ciliberto, Dr Fusco and Dr Bojan carried out the initial analysis of data and critically reviewed the initial manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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