A successful treatment of a severe pulmonary arterial hypertension in a 2-month-old female with incontinentia pigmenti. A case report and review of literature.

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INTRODUCTION

Incontinentia pigmenti (IP) is a rare X-linked dominant neuroectodermal dysplasia, usually lethal in males before birth. Females survive because of X-inactivation mosaicism. IP is caused by a loss-of-function mutations in the IKBKG gene, formerly known as NEMO, located on the Xq28 locus of the X chromosome. The NEMO gene is a kinase subunit that activates the NF-κB pathway, which helps to prevent TNF-α-induced cell apoptosis by regulating the expression of genes related to the immune system, inflammation, cell adhesion and apoptosis. IP occurs in approximately 1:40,000 to 1:50,000 births. It has a global incidence of 27.6 new cases per year worldwide: 65% to 75% are sporadic mutations, while 25% to 35% are familial.

In the classic presentation, cutaneous lesions are the first manifestation, appearing at birth or in the first few months of life, and evolve through 4 peculiar, overlapping stages: vesiculobullous, verrucous, hyperpigmented, and atrophic/hypopigmented lesions that correlate with typical histopathologic changes. These cutaneous lesions in all stages tend to affect Blaschko lines.

IP involves primarily skin but can also affect skin appendages, teeth and the oral cavity, central nervous system, eyes, and blood cells. More rarely, cardiovascular abnormalities (such as ASD, tricuspid insufficiency, abnormal shunt of the right PV into SVC or left ventricular endomyocardial fibrosis causing severe mitral regurgitation) and/or pulmonary hypertension have been reported in infants with IP. Only six cases of pulmonary arterial hypertension (PAH) without associated congenital heart diseases have been described in IP patients until now. Four of them died before one year of age.

Herein we report the third case of successful treatment of severe PAH in a 2-month-old female infant with IP.

OUR CASE

In our case, we had a sudden worsening of PAH that required a severe combined therapy with oral vasodilators (Sildenafil and Bosentan) and intravenous Iloprost plus an anti-inflammatory treatment with intravenous bolus of mPDN and subcutaneous weekly Etanercept injections. The therapy we started is similar to that used by Atallah et al. Unfortunately, we had to stopped Entanercept and Iloprost after few administrations because of an important pulmonary bleeding that required reintubation, evacuative thoracentesis and broad-spectrum anti-infective therapy. After 40 days of PCICU hospitalization our patient progressively improved and was transferred to Cardiological ward, where she was discharged with double oral anti-hypertensive pulmonary therapy (Bosentan and Sildenafil).

In the follow-up, the evolution was favorable with progressive improvement of the PAP confirmed by RHC after 4 and 12 months [Table1]. PAH drugs were tapered down, and finally all PAH treatments were stopped after 24 months. Subsequent controls including physical exams and echocardiograms did not show signs of PAH. The girl is now 3 years old, and she is still undergoing a multidisciplinary follow-up for neurological retardation in the absence of seizures and ophthalmological examinations for ocular anomalies.

OUR RESULTS

	Basal right heart catheterization (RHC)	RHC after 4 months of anti-hyperetensive therapy	RHC after 12 months of anti-hyperetensive therapy
RV [mmHg]	50/6	34/11	26/7
Estimated PAP [mmHg]	51	32	24
mPAP [mmHg]	41	22	19
PCW [mmHg]	2	7	10
dAo [mmHg]	51/28/39	62/33/48	80/30*
CI [l/m/mq]	4,09	5,8	4,13
PVRi [WU/mq]	9,54	4,46	2,18
Rp/Rs	1,05	0,19	-

Table 1. Hemodinamic findings before aggressive combination therapy (anti-hypertensive therapy with bosentan, sildenafil, inravenous iloprost and anti-inflammatory treatment with intravenous bolus of methylprednisolone and subcutaneous weekly Etanercept injections) compared to datas after 4 months and 1 year of double anti-hypertensive pulmonary therapy (bosentan and sildenafil) in our case.
RV, right ventricle; estimated PAP, pulmonary arterial systolic pressure; mPAP, mean pulmonary pressure; PCW, pulmonary capillary wedge, dAo, descending aorta; CI, cardiac index; PVRi, pulmonary vascular resistance indexed; Rp/Rs: pulmonary to systemic resistance ratio.
* non-invasive measurement

DISCUSSION and CONCLUSION

This case suggests that aggressive therapy combining vasodilators and anti-inflammatory treatment for PAH might change the course of this devastating complication in IP. Certainly, further investigations are needed to give a more detailed understanding of the pathophysiology and refining the treatment of PAH associated with IP.

BIBLIOGRAPHY

1.Miteva L, Nikolova A. Incontinentia pigmenti: a case associated with cardiovascular anomalies. *Pediatr Dermatol*. 2001;18(1):54-56.
2.Alshenqiti A, Nashabat M, AlGhoraibi H, Tamimi O, Alfadhel M. Pulmonary hypertension and vasculopathy in incontinentia pigmenti: a case report. *Ther Clin Risk Manag*. 2017;13:629-634.
3.Onnis G, Diociaiuti A, Zangari P, et al. Cardiopulmonary anomalies in incontinentia pigmenti patients. *Int J Dermatol*. 2018;57(1):40-45.
4.Hayes IM, Varigos G, Upjohn EJ, Orchard DC, Penny DJ, Savarirayan R. Unilateral achieiria and fatal primary pulmonary hypertension in a girl with incontinentia pigmenti. *Am J Med Genet A*. 2005;135(3):302-303.
5.Godambe S, McNamara P, Rajguru M, Hellmann J. Unusual neonatal presentation of incontinentia pigmenti with persistent pulmonary hypertension of the newborn: a case report. *J Perinatol*. 2005;25(4):289-292.
6.Yasuda K, Minami N, Yoshikawa Y, Taketani T, Fukuda S, Yamaguchi S. Fatal pulmonary arterial hypertension in an infant girl with incontinentia pigmenti. *Pediatr Int*. 2016;58(5):394-396.
7.Atallah V, Meot M, Kossorotoff M, et al. A case of reversible pulmonary arterial hypertension associated with incontinentia pigmenti. *Pulm circ*. 2018;8(4):1-3.
8.Mizuno M, Aso K, Tsuzuki Y, et al. A successful treatment of tadalafil in incontinentia pigmenti with pulmonary hypertension. *European Journal of Medical Genetics*. 2020;63(3):103764