

New directions in the pathogenesis of primary erythrocytosis in IgAN

Francesco Paolo Skena,^{a*} and Sharon Natasha Cox^b

^aDepartment of Emergency and Organ Transplantation, University of Bari, Bari, Italy

^bDepartment of Biosciences, Biotechnology and Biopharmaceutics, University of Bari, Bari, Italy



Immunoglobulin A nephropathy (IgAN) is the most common biopsy-proven glomerulonephritis in the world.¹ The disease is caused by reduced number of O-glycans in the hinge region of IgA₁ (Gd-IgA₁) and sequential formation of IgG auto-antibodies that link Gd-IgA₁ forming circulating immune complexes that deposit in the mesangial area of glomeruli.² IgAN may be associated with other diseases³ as well as idiopathic polycythemia/erythrocytosis observed in some IgAN patients referenced in Table 1.

Idiopathic polycythemia/erythrocytosis (PE) is a hematological disorder characterized by an overproduction of erythrocytes and can be detected with the increase of some common laboratory parameters i.e hematocrit, hemoglobin (Hb), or red blood cell count. This condition may originate from somatic mutations in hematopoietic progenitor cells or other mutations that induce erythropoietin hypersensitivity.

Cohen et al. describe, in this issue, the association of primary erythrocytosis with IgAN in six biopsy-proven IgAN patients, identified in two multicenter retrospective cohorts of patients with chronic kidney disease or with kidney transplant.⁴ They compared PE prevalence and Hb levels in biopsy-proven IgAN with a large cohort of patients with other types of glomerulonephritis, polycystic kidney disease, and diabetes nephropathy and found a higher prevalence of PE (3.5%) in IgAN patients. The patients had increased serum levels of polymeric IgA₁ and Gd-IgA₁. The researchers studied the effect of polymeric IgA₁ and Gd-IgA₁, isolated from the serum of these patients, on the proliferation and differentiation of erythroid progenitors. Interestingly, they found that polymeric IgA₁ and Gd-IgA₁ increased *in vitro* the sensitivity of erythroid progenitor cells to erythropoietin that was confirmed *in vivo* by an increased hematocrit in alpha knock-in mice that are IgA₁ humanized mice. The authors

concluded that idiopathic erythrocytosis may be caused by polymeric Gd-IgA₁ and the association, IgAN and idiopathic erythrocytosis, should be better investigated in some cases of unexplained erythrocytosis.

Twenty years ago, Moura et al.⁵ described an upregulation of the transferrin receptor (TfR) in human mesangial cells of IgAN patients and polymeric but not monomeric IgA₁ interacted with this receptor confirming that it serves as mesangial IgA₁ receptor for the deposition of polymeric IgA₁ with aberrant glycosylation. Later, Coulon et al.⁶ demonstrated that human polymeric IgA₁ interact with transferrin receptor 1 (TfR1) expressed on the surface of erythroid progenitor cells in mice expressing human IgA₁ compared to control mice and polymeric IgA₁ accelerated recovery from acute anemia after hypoxic stress. Thus, they concluded that the interaction of polymeric IgA₁ and TfR1 increases the sensitivity of erythroid progenitor/pre-cursor cells to erythropoietin. In fact, IgAN patients in the study of Cohen et al.⁴ had normal serum levels of erythropoietin but they presented erythrocytosis. Moreover, the preincubation of IgA₁, eluted from serum of IgAN patients affected by erythrocytosis, with soluble TfR1 increased the binding of erythropoietin to erythroid cells. In conclusion, IgA₁-TfR1 interaction may be involved in the erythropoiesis of IgAN patients.

The work of Cohen et al.⁴ suggests some hypotheses. First, high levels of serum polymeric IgA₁ and/or Gd-IgA₁ may influence erythrocytosis; this event is not rare and therefore other unknown factors may be responsible for the PE/IgAN association and should be uncovered. Second, the *in vivo* and *in vitro* studies have demonstrated that the interaction of polymeric IgA₁ and Gd-IgA₁ with TfR1 could increase the binding of erythropoietin to erythroid cells, but this interaction has not been proved in humans. Third, the EPO levels were normal in IgAN patients with and without erythrocytosis. This means that the increased sensitivity of the erythroid cells to erythropoietin in some IgAN patients might depend on an abnormal expression of TfR1 on the surface of erythroid progenitors. Factors causing this abnormal expression should also be investigated. It might be interesting to study the dynamic expression of the TfR1 on the erythroid cells during the course of the IgAN. Fourth, intracellular signaling studies on pro-erythroblasts after the binding of polymeric IgA₁ and Gd-IgA₁ to erythroblasts could shed more light into the underlying mechanisms associated with PE and IgAN. PI3K-AKT and MAPK-ERK intracellular pathways have

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Abbreviations: Erythrocytosis, IgA nephropathy, Gal-deficiency IgA₁, Polymeric IgA₁, Transferrin receptor 1

*Corresponding author.

E-mail address: paolo.skena@uniba.it (F.P. Skena).

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Reference	Year	No. of Cases	SexM/F	Ageyears	sCr mg/dL	Proteinuriag/day	Htc %	Hbg/dL	RBC10 ⁶ /μl
Kim et al.	1994	1	M	56	1.3	7.8	-	22.1	-
Kasuno et al.	1997	1	M	35	1.6	4	62.8	21.6	6.68
		1	M	31	1.0	2.8	60.0	20.6	7.66
Kwon et al.	1999	1	M	32	10	5.3	-	17.8	-
Chung et al.	2002	1	M	46	2.7	9.1	67.3	21.7	8.17
Yaguchi et al.	2005	1	M	55	2.5	6.9	60	20	6.50
Tian et al.	2011	1	M	56	1.1	13	-	-	-
Chen et al.	2015	1	M	57	1.2	2.8	-	20.7	-
Mahesh et al.	2017	1	M	31	2.2	7.5	-	19.2	-
Navaradnam et al.	2021	1	M	35	3.2	9.0	56.9	20.4	4.50

Table 1: Cases of IgA nephropathy associated with idiopathic polycythemia/erythrocytosis.
Htc: hematocrit; RBC: red blood cells; sCr: Serum creatinine.

been investigated but other intracellular signaling pathways might be involved. Fifth, whole exome or targeted deep sequencing of specific genes involved in erythroid cell proliferation or clonal expansion⁷ should be performed on large cohorts of IgAN patients and may be the best strategy to analyze rare somatic variant effects responsible for the development of PE in some IgAN patients. Last but not least, this important study does not report the exact time point of the PE/IgAN association, furthermore these patients' clinical course and outcome should be compared with IgAN patients without PE. It is essential to study this association on a larger scale and to answer some simple questions: does the PE/IgAN association confer a higher risk for thromboembolic events as seen in PE patients?^{8,9} Should these patients be treated with antithrombotic drugs?¹⁰ These studies are mandatory and can influence future clinical and therapeutic decisions making for this, non-rare, subset of patients.

In summary, the work of Cohen et al.⁴ brings up many challenges inherent the development of erythrocytosis in IgAN patients, such as the important role of TfR1 on the surface of erythrocytes and highlights an urgent need to conduct new studies on a large population of IgAN patients with associated erythrocytosis. This may be a call for researchers involved in the clinical and molecular studies in IgAN patients because IgAN may be an independent factor associated to higher levels of hemoglobin, and patients are at high risk to develop erythrocytosis. Further work is also needed to define the mechanism of polymeric Gd-IgA1 on the TfR1 in human erythrocytes.

Declaration of interests

The authors declare no conflicts of interest.

Contributors

FPS: Literature search, study design, data collection, data interpretation, writing

SNC: Literature search, data interpretation, writing

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