Morphological Spectrum of Paroxysmal Nocturnal Hemoglobinuria (PNH)

Kanjaksha Ghosh

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Sir,

Morphological spectrum of paroxysmal nocturnal haemoglobinuria (PNH) is very heterogenous, at one extreme a patient will be diagnosed with hypercellular marrow with unusual thrombosis and mild anaemia and on the other we see a severely aplastic bone marrow with clinical features of PNH and while in some other a diagnosed aplastic anaemia patient with time evolves into PNH like disease. The moot question is whether these diseases are different manifestations of the same disease caught at different time point of their natural history or they are different diseases altogether?

Natural history of PNH has been now been studied in a few well controlled studies [1, 2]. Hillmen et al. [1] showed spontaneous remission in a proportion of these cases on long follow up, a median survival of 10 years and thrombosis and haemorrhage as the major cause of death. Hence the author cautioned against giving potentially dangerous treatment in these patients. Latour et al. [2] describing the natural history of PNH with a large cohort of PNH patients extending over half a century.

Significant advances in the understanding marrow failure syndromes have now been made and availability of sensitive techniques for detection of PNH clone by flow cytometry make it easier to detect the disease very early in its course.

Many studies have shown the overlap of these syndromes at diagnosis [2–4] and progression of one to

another morphological group making it very difficult to uniformly classify these patients.

The international PNH interest group, came up with guidelines for diagnosis and classification of PNH syndromes in 2005 [5]. Though the study by de Latour et al. [2] has followed the same guidelines, it has not classified the patients with past history of Aplastic anaemia (AA) into AA–PNH group, but rather classified the cases depending on the clinical presentation at the time of diagnosis of PNH.

One interesting finding in the study [2] is discrimination of morphological types of PNH which have been described as AA–PNH and classical PNH, as they have shown different hazard ratio for survival, transfusion requirement and thrombosis.

However in this large series 93/430 (21.3 %) patients showed characteristics which were intermediate between AA–PNH and classical PNH and showed its potential transformation to AML and MDS.

This study and also many others on natural history of PNH [6, 7] have not separately defined any MDS–PNH category. Some of these intermediate-PNH patients may fall into what we have been referring as MDS–PNH category on the basis of marrow morphology, cytogenetics and natural history.

Nuances of diagnosis also change with time as aplastic marrow was shown to be associated with PNH like clone at some point of time in the natural history of AA even without sensitive flowcytometric technique to detect PNH clone. These cases were not regarded as PNH as overt symptoms of PNH were not seen. Today even presence of 0.01 % PNH clone would be sufficient to diagnose PNH [8] even without any of the classical PNH symptoms. Because of these changes in nuances of diagnosis and early diagnosis of the disease, many such diseases are showing significant prolongation of median survival compared to historical studies.

K. Ghosh (✉)
National Institute of Immunohaematology (ICMR), KEM
Hospital, 13th Floor, NMS Bldg, Parel, Mumbai 400012, India
e-mail: kanjakshaghosh@hotmail.com

Fig. 1 Putative pathways linking Bone marrow injury to AML Acute Myeloid Leukemia, AA aplastic Anemia, AA-PNH Aplastic anemia with PNH, MDS Myelodysplastic Syndrome, MDS-PNH Myelodysplasia with PNH

We have studied a much smaller cohort of 33 patients, diagnosed over 3 years. The morphology of marrow aspirate and trephine biopsy were reviewed independently of the knowledge of cytogenetics. Diagnosis of PNH in all our patients were done by flow cytometry with CD55 and CD59 expression on granulocytes and red blood cells [9]. Our morphological and cytogenetic findings suggested that PNH can be classified as classical PNH (13/33), AA-PNH (13/33) and third category fitted into MDS-PNH (7/33) rather than intermediate-PNH as described elsewhere [2], due to either evidence of significant dysplasia and/or cytogenetic abnormalities. There was also transformation of AA-PNH to MDS-PNH over time and vice versa (Fig. 1). One of our patients diagnosed as classical PNH with history of occupational exposure to benzene like chemical for several years, showed a rapid progression to MDS and then to AML over a period of 6 months only, showing that transformation of PNH to acute leukaemia though rare does occur. Two patients in our series with cerebral venous and one with intra-cardiac thrombi died.

Natural history of PNH clones in patients presenting with aplastic anaemia has recently been studied with relationship to thrombosis, haemoglobinuria [6]. It was found in subsequent studies that a PNH clone of granulocytes more than 61 % were associated with high risk of thrombosis, an erythrocyte clone size of >3–5 %, of granulocyte clone size of >23 % correlated well with elevated LDH levels[10]. In 25 % of cases clone size decreased on long follow up. Presence of PNH clone in aplastic anaemia also improves therapeutic outcome following immunosuppressive therapy [11].

Hu et al. [12] showed PIG-A mutation is not uncommon in normal haematopoiesis when studied in vitro. Normal healthy adults can show 0.002–0.003 % PNH positive granulocytes as well as PNH positive lymphocytes [13]. Hence PNH clones are naturally produced in bone marrow in small numbers but with change of marrow environment when some growth advantage accrues to PNH clone, the clone develop into a dominant clone and cause PNH symptoms.

It may be argued that following bone marrow damage the progenitor cells/stem cells as they proliferate in adverse environmental circumstances PNH positive clones which tends to resist apoptosis could emerge [14] as the dominant clone. If the clone size with aplastic anaemia is very small and is not increasing in size over time it denotes that the marrow microenvironment is not suitable for development of full fledged PNH [10, 15].

Following marrow injury depending on severity and nature of the injury marrow may completely recover, may not recover at all leading to aplastic anaemia, or during the course of protracted recovery PNH clones may emerge along with MDS like picture or without MDS and finally a small proportion of these cases may progress to AML.

Hillmen [1] has not noted any AML in his series of 80 cases over protracted period we and others have noted that AML indeed develops in a small proportion of such cases. As our diagnostic tests [16] improve it is possible that we will be able to detect each of the nuanced diagnosis at points in the natural history of PNH when management can be individualized.

In Fig. 1 we have depicted the natural history of PNH and PNH like clones in aplastic anaemia as we found in our study.

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Conflict of interest None.

References

1. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV (1995) Natural history of paroxysmal nocturnal haemoglobinuria. *N Engl J Med* 333:1253–1258
2. de Latour RP, Mary JY, Salanoubat C, French Society of Hematology, French Association of Young Hematologists et al (2008) Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood* 112(8):3099–3106
3. Mukhina GL, Buckley JT, Barber JP, Jones RJ, Brodsky RA (2001) Multilineage glycosylphosphatidylinositol anchor deficient

- hematopoiesis in untreated aplastic anemia. *Br J Haematol* 115: 476–482
4. Masako I, Koichi F, Tatsuhiko A (1998) Paroxysmal nocturnal clone in patients with myelodysplastic syndrome. *Br J Hematol* 102(2):465–474
 5. Parker C, Omine M, Richards S, Nishimura J-I, Bessler M, Ware R, Hillmen P, Luzzatto L, Young N, Kinoshita T, Rosse W, Socie G, International PNH Interest Group (2005) Diagnosis and management of paroxysmal nocturnal haemoglobinuria. *Blood* 106:3699–3709
 6. Moyo VM, Mukhina GL, Garrett ES, Brodsky RA (2004) Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. *Br J Haematol* 126(1):133–138
 7. Nishimura JI, Kanakura Y, Ware RE et al (2004) Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine (Baltimore)* 83: 193–207
 8. Brodsky RA (2006) New insights into paroxysmal nocturnal hemoglobinuria. *Hematol Am Soc Hematol Educ Program* 516: 24–28
 9. Richards SJ, Rawstron AC, Hillmen P (2000) Application of flow cytometry to the diagnosis of paroxysmal nocturnal hemoglobinuria. *Cytometry* 42:223–233
 10. Pu JJ, Mukhina G, Wang H, Savage WJ, Brodsky RA (2011) Natural history of paroxysmal nocturnal haemoglobinuria clones in patients presenting as aplastic anaemia. *Eur J Haematol* 87: 37–45
 11. Sigimori C, Chujho T, Feng X et al (2006) Minor population of CD55-CD59 blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. *Blood* 107:1308–1314
 12. Hu R, Mukhina GL, Piantadosi S, Barber JP, Jones RJ, Brodsky RA (2005) PIG-A mutation in normal haemopoiesis. *Blood* 105: 3848–3854
 13. Ghosh K (1994) How immature is the abnormal stem cell in paroxysmal nocturnal hemoglobinuria? *Am J Hematol* 47:245
 14. Savage WJ, Barber JP, Mukhina GL et al (2009) Glycosyl phosphatidylinositol-anchored protein deficiency confers resistance to apoptosis in PNH. *Exp Hematol* 37:42–51
 15. Sugimori C, Mochizuki K, Qi Z et al (2009) Origin and fate of blood cells deficient in glycosylphosphatidylinositol anchored protein with bone marrow failure. *Br J Haematol* 147:102–112
 16. Madkaikar M, Gupta M, Jijina F, Ghosh K (2009) Paroxysmal nocturnal haemoglobinuria: diagnostic tests, advantages, & limitations. *Eur J Haematol* 83:503–511