Blood group A_{int} causing uncertainty during organ donor work-up for incompatible (A_2-O) liver transplantation

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Dear Sir,

The ABO blood group system, discovered more than a century ago, still often raises uncertainty among immunohaematologists during subtyping or detection of weak variants. A_1 and A_2 are the major subgroups of blood group A which are differentiated on the basis of reactivity of A_1 cells but not A_2 cells with anti-A_1 lectin (*Dolichos biflorus*)[1]. Routine subgrouping of all A and AB blood groups in India is limited to a few blood centres because of economic constraints and this subgrouping is usually performed only when there is a group discrepancy, a problem during compatibility testing or a history of a transfusion reaction. The role of subtyping group A is, however, critically important when it is being done for (A_2-O) incompatible organ transplantation.

There are a few studies on weak subgroups of the ABO system but the prevalence and occurrence of the "A-intermediate" (A_{int}) subgroup in India are underreported and have not been published in recent decades. We report here the case of A_{int} subgroup encountered in two siblings during the pre-transplant work-up of an incompatible live donor liver transplant.

A 34-year old female patient, resident in Kerala, was admitted to the Liver Transplant and Hepato-Biliary Department with features of acute on chronic liver disease due to Wilson's disease; a liver transplant was planned. Samples from the patient and two siblings were subjected to urgent blood grouping and subtyping in the Immunohaematology Laboratory of our Blood Bank. During blood grouping, forward grouping was done using gel technology (Diaclon, Diamed ID, Switzerland) while reverse grouping was performed using in-house prepared pooled A, B and O cells. All the laboratory techniques were carried out according to the manufacturer's instructions. Blood groups were interpreted based on the agglutination pattern with forward and reverse grouping. The recipient's blood group was O-positive and both siblings were A-positive. Considering the possibility of incompatible (A_2-O) liver transplantation, the siblings were further subtyped using anti-A_1 lectin (Diamed AG, Cressier sur Morat, Switzerland) to classify them into A_1 or A_2.

Using a tube method with A_1 lectin, both siblings showed 1- 2+ positive agglutination. A provisional report of A_1 subtype was given to both siblings. Due to the weak reaction with A_1 lectin, the sample was further tested by H lectin (Tulip Diagnostics, Goa, India) which gave a strong 4+ reaction favouring towards an A_2 subtype. Bearing in mind the possibility of false positive results, we checked the potency and specificity of the A_1 and H lectins using control A_1, A_2 and O cells. The titres of A_1 lectin and H lectin were 1:16 with standard A_1 and O cells, respectively. Saliva inhibition studies performed on both the siblings showed the presence of A and H substances. The blood groups of both siblings were reported as A_{int} and the previous reports of A_1 subtype were withdrawn. As the antigenicity of this subgroup was likely to be higher than that of A_2, both the siblings were cancelled from the potential liver donor list. Blood samples from the patient's parents were also tested, given the possibility of A_{int} in other family members. In this family, the parents' blood groups were A_1 and O group; A_{int} was present only in the two siblings.

A_1 and A_2 differ from each other both qualitatively and quantitatively, with A_1 cells carrying 8.1 to 11.7×10^5 antigenic sites as compared to 2.4 to 2.9×10^5 sites on A_2 red blood cells. The prevalences of A_1, A_2 and weak subgroups in South India were recently reported to be 98.4%, 1.85% and 0.01%, respectively[2].

There are reports of safe and successful liver transplants from A_2 blood group donors to O blood group recipients, without plasmapheresis or rejection. The role of subtyping the A blood group has gained importance since the beginning of ABO incompatible organ transplantation. There are, however, cases reports of accelerated acute rejection of A_2 renal allografts in O recipients which might have resulted from misapplication of the results of standard lectin agglutination to the transplant setting, highlighting the importance of subtyping the A group. More sophisticated methods of ABO phenotyping, such as erythrocyte flow cytometric analysis, have been suggested in the transplant setting[3].

The existence of an additional subtype of A, which exhibited characteristics intermediate between A_1 and A_2 (A_{int}), was first recognised by Landsteiner and Levine[1]. While Brain's classification was based on weaker reactions (+ or ++) with *Dolichos,* with H (*Ulex*) reactivity stronger than A_2[4], the "A_{int}" designated by

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BIRD[5] suggested stronger reactivity with both *Dolichos* and *Ulex*.

A_{int} is a heterogeneous subgroup which is more common in black people than in white ones. Of group A African-Americans, 8.5% were found to be A_{int} compared with about 1% of group A white Americans and 2.5% of group A Caucasians. Of group A black South Africans 13.7% were A_{int} [4]. The incidence of A_{int} in India was reported to be 2% in group A Maharastrians[5]. It is likely that the incidence may vary in different endogamous caste groups of India and needs extensive study.

No detailed study has so far been reported to elucidate the nature of inheritance of this subgroup. Some studies reported A_{int} phenotype in two generations during family studies and concluded that A_{int} is likely to be inherited by a separate allele. However in other family studies, A_{int} was present in siblings but not in parents. Transmission of at least one strong H gene from parents to their children partnered by an A_1 gene could give the serological picture of A_{int} blood group with large H antigen. This is compatible with our case in which both the siblings were A_{int} while the father was A_1 group and the mother O group.

The expression of different A subtypes in red blood cells is the consequence of diverse formations of the A substances by the action of three types of blood group N-acetyl-galactosaminyl-transferases controlled by A_1, A_2, and A_{int} genes. The A subtypes are, therefore, more directly identified by examining the kinetic characteristics of A-enzymes in the plasma. A molecular characterization or enzyme analysis would have been useful but could not be performed in this case. Our report points to the need to confirm some cases by molecular tests or by flow cytometric analysis, especially in the organ transplant setting in India. We also recommend the mandatory use of H lectin when subtyping for A to avoid mistyping and errors of interpretation.

The Author declares no conflicts of interest.

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