Recovery of Hair Coat Color in Gray Collie (Cyclic Neutropenia)-Normal Bone Marrow Transplant Chimeras

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Gray Collie-normal bone marrow transplantation chimeras showed normal coloration of the hair coat on tails and several other areas 2 years after successful transplantation of bone marrow to correct cyclic neutropenia of the Gray Collie syndrome. (Am J Pathol 91:149–154, 1978)

GRAY COLLIE SYNDROME is a lethal hereditary disorder associated with gray-silver hair coloration in English Collies (Figure 1). The coat color ranges from dark pewter gray to silver. The shade depends on the hair color genotype of the dam and sire, ie, whether the offspring inherited sable or tricolored genotype.[1-3] Nearly half of the pups die within a few days of birth or are stunted in growth. Those that survive are overly susceptible to a wide range of bacterial and fungal infections and seldom live past the age of 3 months unless intensive medication against recurrent infections is given. Dogs maintained by electrolyte therapy and antibiotics may survive to 2 or more years of age but develop anemia, chronic arthritis, amyloidosis, glomerulonephritis, and lymphoid exhaustion.[4,5]

The Gray Collie syndrome is associated with several abnormalities such as abnormal hair pigmentation; cyclic changes in most of the formed blood elements, especially neutrophils; and humoral regulators of hematopoiesis, enteropathy, and gonadal hypoplasia.[6-11] Cyclic neutropenia is responsible for most of the signs of periodic disease. Severe neutropenia occurs at intervals of 12 ± 1 days with episodes of fever, diarrhea, gingivitis, respiratory infection, lymphadenitis, and arthralgia following neutropenia phases. The syndrome is remarkably similar to that of human cyclic neutropenia which cycles at approximately 21 days.[6,12] Genetic studies of Lund et al [2] indicate that the disease is caused by an autosomally recessive gene with pleiotropic effect on coat color dilution or that

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the hematologic disease is closely linked with the gray coat color gene. The wide spectrum of clinical signs and lesions in the Gray Collie syndrome seems to be due to basic defects in bone marrow, as demonstrated by bone marrow transplantation studies. Following transplantation of the normal marrow, dogs with Gray Collie syndrome experienced no further cycles of neutropenia. Conversely, the unaffected littermates, transplanted with marrows from Gray Collies, became affected with the cyclic rise and fall of blood cells subsequent to engraftment.[13-15]

This paper reports the unexpected recovery of the hair coat color on tails and several other areas in Gray Collie/normal bone marrow transplant chimeras 2 years after the successful bone marrow transplantation to correct cyclic neutropenia of the Gray Collie syndrome.

Materials and Methods

Animals

The Gray Collie (cyclic neutropenia)/normal bone marrow transplant chimeras CH309 and CH310 have been described previously.[15] They were Collie–Beagle genotype dogs with gray and white hair coat color and well-documented cyclic neutropenia before transplantation at the age of 170 days. The bone marrow donors were normal-appearing littermates matched for serologically defined (SD) and lymphocyte-defined (LD) histocompatibility antigens. Complete normalcy of the donor littermates from heterozygous parents could not be determined since the only method available for detecting carrier state is by test mating.

Bone Marrow Transplantation

Bone marrow transplantation was done after supralethal irradiation of recipients with 1250 rad from ^{60}Co sources at 9 rad/min.[16] Female CH309 received 7.73×10^9 bone marrow cells from normal male littermate N315; male CH310 received 5.07×10^9 bone marrow cells from normal male littermate N316. Sex chromosome marker studies indicated, at least in CH309, that the circulating peripheral blood cells after transplantation are of donor origin. No immunosuppressive agents were administered during the postgrafting period, and bone marrow engraftment was evidenced by rising peripheral leukocyte and platelet counts after 10 days. By the 35th day, total leukocyte counts were within normal range and their cycles of neutropenia ceased. Their immunologic competence was found to be normal when transplanted with allogeneic tumor grafts 10 months later.

Ten months after the bone marrow transplantation, CH309 and CH310 received third-party allogeneic canine transmissible venereal sarcoma cells (4×10^7 viable cells) subcutaneously. The tumor grew after 16 days and started to regress after 2 (CH310) to 3 months (CH309), as in other normal dogs of comparable age.[17]

Results

After the successful bone marrow transplantation to correct cyclic neutropenia in Gray Collies, the dogs have been kept for use in the study of immunologic mechanism of long-term chimeric state. During the observation period, the dogs were housed together in a pen at the University of Connecticut Spring Hill Isolation Farm and fed Purina Field and Farm

dog food. The room temperature was kept at approximately 65 to 75 F. Daylight periods ranged from 10 to 15 hr/day. No immunosuppressive agents have been administered and no recognizable signs of graft-versus-host disease or rejection of the bone marrow grafts have been noted to date, ie, 3.5 years after transplantation. This success may be attributed partly to good histocompatibility matching and to the fact that peripheral blood mature leukocytes in the bone marrow cell suspensions were kept minimal by complete exsanguination prior to long bone marrow collection.[18]

Unexpectedly, at 2 years after transplantation (spring, 1976), the hair coat color of both dogs started to change to normal brown color on four fifths of the tail and part of the postscapular and prefemoral areas on both sides. Both parents of CH309 and CH310 were tricolor and the littermates of CH309 and CH310 would have tricolor genotype. The brown color may thus represent incomplete change.

The color is more intensive at terminal or subterminal areas of individual hairs, as in normal hair. Probably due to topographic variation of skin and hair follicle activity, the color of the tail was more intense, especially that of CH309, than that of the other parts. It has remained so for CH309 even to date (3.5 years after transplantation) (Figure 2). The color on the tail and other parts of CH310, however, became appreciably diluted 2.5 years after transplantation (fall, 1976) and has remained so to date.

Discussion

The mechanism of recovery of hair coat color is unknown; it is especially unclear how the bone marrow cells affect the coat color of the hair. It happened in both of the chimeras, but not in the four Gray Collies that did not receive bone marrow transplants and that survived 2 or more years,[4,19] indicating that the phenomenon is not coincidental. A "super stem cell" in the donor bone marrow, the mutagenic effect of radiation, or the occurrence of metabolic cooperation between the donor cells and recipient hair follicle cell may be involved.[20-22]

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2A

2B

Figure 1—A Gray Collie with typical hair coat color and microophthalmia. **Figure 2**—Hair coat color change in chimera CH309 cured of Gray Collie disease (cyclic neutropenia) by transplantation of normal bone marrow 3.5 years ago. **A**—Whole body photograph showing charcoal gray to off-white hair coat over most of the body, typical of a dog affected with Gray Collie disease. Hair coat color change on the tail started 2 years after normal bone marrow transplantation. **B**—Close-up of the dorsal view of the tail.