INTRADUCTION

Mature articular cartilage shows a limited capacity for regeneration after degeneration or injury. Generally, osteochondral defects are repaired by endochondral ossification. Since the defect filled with reparative cells derived from bone marrow shows many vascular invasions, the defect is replaced by bone. We have previously constructed and transplanted tissue-engineered cartilage (1) into an osteochondral defect, and good restorative effects have been reported in a long-term study (2). We confirmed that, in the early stage of transplantation, good restorative effects of articular cartilage were achieved by reparative cells derived from marrow-acquired properties of antiangiogenesis (3). We thus hypothesized that better cartilage repair may be achieved by inhibiting the bioactivity of vascular endothelial growth factor (VEGF) in the osteochondral defect. The objective of the current study was to investigate the efficacy of repairing an osteochondral defect in rabbit knee joints by administration of bevacizumab, a humanized monoclonal anti-VEGF antibody.

METHODS

Japanese white rabbits (n=36; weight, 3 kg) were used in this study. An osteochondral defect (diameter, 5 mm; depth, 3 mm) was created on the patellar groove of the femur. Rabbits were classified into two recipient groups: Group B, administration of bevacizumab (n=16; 100 mg intravenous injection administered on day of surgery and 2 weeks later); and Controls (n=20; defect only). Rabbits were sacrificed 1 and 3 months postoperatively. Sections were stained with safranin O. Repairing sites were evaluated using the modified O’Driscoll ICRS grading system. Sections were evaluated using immunohistochemical analyses for type I and II collagen, chondromodulin (ChM)-I and VEGF. Differences in histological scores were assessed using the Mann-Whitney U test. Values of P<0.01 were accepted as statistically significant.

RESULTS

At 1 month after surgery, in Group B, the repair site appeared to be filled with cartilaginous tissues (Fig. 1A-D). At 3 months, the repair site kept the phenotype of cartilage (Fig. 2A-D). At 1 month in Controls, defects were filled with mainly fibrous tissue (Fig. 1E-H). At 3 months, the defect was replaced by fibrous tissue and bone (Fig. 3A-D). Over the 3 months, histological scores were significantly higher in Group B than in Controls (Fig. 6). At 1 month, Group B showed intense positive results for ChM-I in the bottom of the repair tissue (Fig. 4A, B). VEGF was also identified in the same area (Fig. 5A). In Controls, no ChM-I was observed in repair tissue (Fig. 4C). Conversely, the remodeling hypertrophic chondrocyte layer was intensely positive for VEGF (Fig. 5B).

DISCUSSION

VEGF is overexpressed by numerous solid angiogenic tumors and hematological malignancies. Interrupting the VEGF pathway has thus become a major focus of oncological research (4). The most successful antiangiogenic approach is bevacizumab, a humanized monoclonal anti-VEGF antibody. Bevacizumab broadly represents a major advance in antiangiogenic therapy (5). We reported herein cartilage repair effects following intravenous administration of bevacizumab as an anti-VEGF antibody for osteochondral defects. As a result, a good process of cartilage repair was confirmed within 3 months postoperatively. Interestingly, expression of ChM-I was acquired in the early stage of the repaired tissue after bevacizumab administration. Expression of ChM-I in this study inhibited vascular invasion from subchondral bone, indicating that ChM-I preserved a function to acquire expression of the characteristics of articular cartilage.

CONCLUSION

Intravenous administration of bevacizumab contributed to the repair of articular cartilage in the osteochondral defect model.

REFERENCES