Case Report

Magnetic resonance imaging of the bone marrow in 3 patients with aplastic anemia

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ABSTRACT

Bone marrow appearances in aplastic anemia are characterized by the abundance of fatty marrow that replaces normal functional marrow. The signal intensity of aplastic bone marrow in sagittal T1-weighted magnetic resonance images of the spine is bright, resembling that of subcutaneous fat and, in most cases, is not difficult to differentiate from normal age-related marrow changes. Three patients with aplastic anemia are described, and the correlation of magnetic resonance imaging of the spine with bone marrow trephine biopsy findings in these patients is portrayed. Magnetic resonance imaging is an accessible, non-invasive technique that allows sampling of a larger volume of bone marrow tissue and is especially useful in the detection of fatty marrow replacement of the normal functional marrow in aplastic anemia.

Keywords: Aplastic anemia, fatty marrow, magnetic resonance imaging.

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Magnetic resonance (MR) imaging of the bone marrow (BM) is becoming a useful complement to bone marrow aspiration and trephine biopsy in the diagnosis, staging and follow-up of bone marrow diseases.[1-3] Aplastic anemia is either a constitutional (e.g. Fanconi) anemia or an acquired condition which could be due to toxic, infectious, metabolic, immunologic or other causes. Whatever the cause there is a stem cell failure and functional marrow is replaced by non-functional fatty marrow. The replacement process starts in a patchy manner at the beginning but, later on it becomes a generalized process leading to generalized marrow failure.[4] Sometimes at presentation only one cell line is depressed but other cell lines will fail shortly thereafter.[4] Aplastic anemia was defined by the International Aplastic Anemia Study Group as bone marrow cellularity of <25%, or cellularity of <50% with <30% hemopoietic cells with at least 2 of the following: neutrophil count of <0.5 x 10^9/L, platelet count <20 x 10^9/L, anemia and a corrected reticulocytes index of <1%.[5] Normal red bone marrow is 40% water, 40% fat and 20% protein. On T1-weighted images it gives a low or hypointense signal similar to or slightly higher than muscles. On the other hand fatty or yellow bone marrow on account of its low water content gives an easily recognizable bright signal resembling that of subcutaneous fat.[2] Trephine biopsy is still regarded as the gold standard in the diagnosis of aplastic anemia. Residual foci of hyperactive marrow can be a problem when making the diagnosis using trephine biopsy alone, and multiple biopsies may be needed to establish the diagnosis. This is an area where MR imaging can be very helpful in reducing the number of biopsies and in sampling a larger volume of the bone marrow. All MR images were performed using spin-echo radio-frequency pulse sequences with the whole-body transmitter/receiver coil in a 1.5 Telsa General Electric Horizon instrument. Sagittal T1-weighted images of the spine were obtained in contiguous (4mm) slices in a 512 x 224 matrix with Relaxation time (TR) = 600 millisecond, Echo Time (TE) = 14 ms and acquisition = 2. T1-weighted

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images were selected because of their ability to distinguish between fatty marrow, which has a high signal because of its short proton T1 and appears bright from normal cellular marrow, which because of its long T1 has a low signal, and appears dark. Patterns recognized in our patients were (1) Fatty marrow (2) Fatty marrow with few cellular foci. Other patterns like inhomogeneously cellular and diffusely cellular, which could also be seen in Myelodysplastic Syndromes (MDS), were not seen in our patients. T2-weighted (fat suppressed) and short time inversion recovery images (STIR) were not selected as they are more useful for distinguishing between aplastic anemia and MDS especially when T1-weighted images show inhomogeneously cellular or diffusely cellular patterns.

Case Report.

Patient 1. A 17-year-old Saudi female with mental retardation and cerebral palsy who was discovered to have thrombocytopenia and granulocytopenia on routine complete blood count (CBC). There was no history of any significant bleeding tendency, recent illness, fever, drug intake or exposure to chemicals. She suffered from constipation and the family history was irrelevant. She had spastic paraplegia, otherwise clinical examination was unremarkable. She had no fever, lymphadenopathy, organomegaly or skin rashes. Investigations revealed hemoglobin (Hb) 12.2 g/dl (normal >12.5), white blood cell (WBC) count 3.15 x 10^9/L (normal 4-11), platelets 8 x 10^9/L (normal 150-450), mean corpuscular volume (MCV) 83.7 fl (normal 80-98), corrected reticulocytes index 0.6% (normal >1.0) and erythrocyte sedimentation rate (ESR) was 5.0 mm/hr (normal <10). White blood cell differential count showed moderate granulocytopenia; neutrophils 1.18, lymphocytes 1.79, monocytes 0.13, eosinophils 0.04 and basophils 0.01 x 10^9/L. Coagulation screen was normal. Antinuclear antibodies, platelet antibodies by direct immunoflourescence and other autoantibodies were all negative. Liver function tests, lactic dehydrogenase (LDH), serum urea and creatinine and serum electrolytes were normal. Screening for viral hepatitis (hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis C virus (HCV)) were negative. Investigations to exclude paroxysmal nocturnal hemoglobinuria (PNH) included neutrophil alkaline phosphatase reaction score of 109 (normal 35-100), while sucrose lysis test, acidified serum test (Ham's test) and urinary hemosidrin were negative. Ultrasound imaging of the abdomen was normal. Cytogenetic study revealed a normal female (46XX). Bone marrow biopsies were taken from the posterior superior iliac spine on both sides; they revealed profound hypocellularity (10%) with fat spaces accounting for 90% of available space between the bony trabeculae on both sides. Few normal lymphocytes, plasma cells and stromal cells could be seen sprinkled around as well as many dilated marrow sinusoids. There was no fibrosis or increased reticulin deposition (Figure 1a). Sagittal T1-weighted (SE 600/14) MR images, showed fatty marrow pattern, with the vertebral bone marrow signal intensity being bright and uniformly increased in comparison with inter-vertebral discs, approaching that of subcutaneous fat, a picture which is consistent with aplastic anemia where functional marrow is replaced by fatty marrow (Figure 1b).

Patient 2. A 23-year-old Saudi male with a short history of pallor, easy fatigability and gum bleeding of insidious onset. There was no history of recent illness, fever, drug intake or exposure to chemicals and family history was irrelevant. Clinical

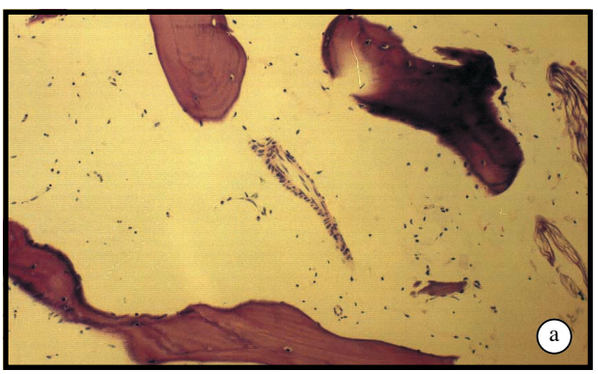

Figure 1 - **(a)** Photographic plate of trephine biopsy from the first patient showing profound hypocellularity with fat spaces accounting for 90% of available space. Low power view, hematoxylene and eosin stain. **(b)** Sagittal T1-weighted magnetic resonance image of dorso-lumbar spine from first patient. Aplastic bone marrow shows fatty marrow pattern, a recognizable bright signal approaching that of subcutaneous fat.

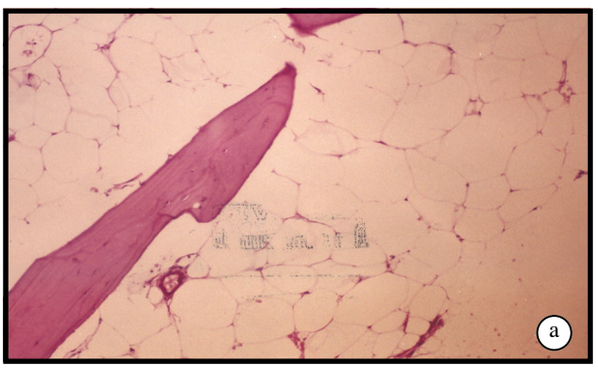

Figure 2 - **(a)** Photographic plate of trephine biopsy from 2nd patient showing profound hypocellularity (<10%). Low power view, hematoxylene and eosin stain. **(b)** Sagittal T1-weighted magnetic resonance image of dorso-lumbar spine from the 2nd patient showing bright signal of fatty marrow. Two spots of low signal intensity are residual foci of normal marrow.

examination revealed a few purpuric spots on the trunk and extremities and gum bleeding but there was no lymphadenopathy or organomegaly. Investigations revealed anemia with Hb 8.0 g/dl (normal >13.5), WBC 3.67 x 10^9/L (normal 4-11), platelets 5 x 10^9/L (normal 150-450), MCV 85.7 fl (normal 80-98) and corrected reticulocytes index 1.5% (normal >1.0). White blood cell differential count showed moderate granulocytopenia; neutrophils 0.91, lymphocytes 2.66, monocytes 0.06, eosinophils 0.02 and basophils 0.02 x 10^9/L. Coagulation screen was normal. Antinuclear antibodies and other autoantibodies were negative, platelet antibodies by direct immunoflourescense was unavailable. Liver function tests, LDH, serum urea and creatinine, serum electrolytes and urine analysis were all normal. Screening for viral hepatitis (HAV, HBV & HCV) was negative. Investigations to exclude PNH included neutrophil alkaline phosphatase reaction score of 306 (normal 35-100), while sucrose lysis test, acidified serum test (Ham's test) and urinary hemosidrin were negative. Hemoglobin electrophoresis showed acquired increase of Hb-F, quantitation of Hb-F by radial immunodiffusion was 6% (normal <0.7). Ultrasound imaging of the abdomen was normal. Bone marrow biopsy taken from the posterior superior iliac spine showed low cellularity (<10%) with few residual lymphocytes, plasma cells and stromal cells recognized in the strands separating the fat spaces. Occasional small foci of residual normal marrow elements could be seen in some sections (Figure 2a). Sagittal T1-weighted (TR-600/TE-14) MR images of the dorso-lumbar spine showed fatty marrow pattern. These revealed a uniform increase of vertebral bone marrow signal intensity, as bright as subcutaneous fat, which is consistent with aplastic anemia. Two spots of dark hypointense signal, that may represent residual foci of normal hematopoietic marrow could be seen (Figure 2b).

Patient 3. A 20-year-old Saudi male with insidious onset of pallor and easy fatigability. Routine CBC showed marked anemia and thrombocytopenia and he was referred to our hospital on steroids. He had no history of recent illness, fever, drug intake or exposure to chemicals and family history was irrelevant. Clinical examination revealed a few purpuric spots on trunk and extremities, just palpable liver but there was no lymphadenopathy or splenomegaly. Investigations revealed anemia with Hb 6.2 g/dl (normal >13.5), WBC 3.17 x 10^9/L (normal 4-11), platelets 6 x 10^9/L (normal 150-450), MCV 101.6 fl (normal 80-98), corrected reticulocytes index 2.1% (normal >1.0) and ESR was 115 mm/hr. White blood cell differential count showed slight granulocytopenia; neutrophils 1.5, lymphocytes 1.59, monocytes 0.07, eosinophils 0.01 x 10^9/L and no basophils. Coagulation screen was normal. Similarly antinuclear antibodies and other autoantibodies were negative, platelet antibodies by direct immunoflourescense was unavailable. Liver function tests, LDH, serum urea and creatinine, serum electrolytes and urine analysis were all normal. Ultrasound imaging of the abdomen was normal. Screening for viral hepatitis (HAV, HBV & HCV) was negative. Tests to exclude PNH included neutrophil alkaline phosphatase reaction score of 319 (normal 35-100), while sucrose lysis test, acidified serum test (Ham's test) and urinary hemosidrin were negative. Hemoglobin electrophoresis revealed acquired increase of Hb-F; quantitation of Hb-F by radial immunodiffusion was 7% (normal <0.7). Bone marrow biopsy taken from the posterior superior iliac spine showed marked hypocellularity, fat spaces accounting for >95% of available space with few residual lymphocytes, plasma cells and stromal cells in the intervening strands. Occasional islands of preserved marrow elements could be seen in some sections. Whether these represented residual active marrow or a partial response to steroid therapy could

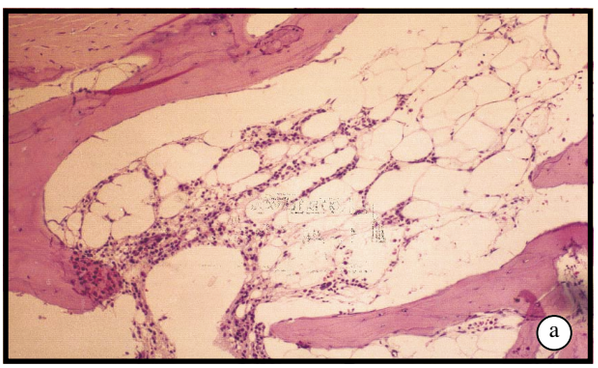

Figure 3 - **(a)** Photographic plate of trephine biopsy from 3rd patient showing profound hypocellularity. Fat spaces account for 95% of available space. Low power view, hematoxylene and eosin stain. **(b)** Sagittal T1-weighted magnetic resonance image of dorso-lumbar spine from the 3rd patient showing fatty marrow with some cellular foci causing heterogeneity of signal density.

not be determined with certainty (Figure 3a). Sagittal T1-weighted MRI study of the lumbar spine showed a pattern of fatty marrow with some cellular foci. It revealed some heterogeneity of bone marrow signal intensity. There were some scattered foci of low or hypo-intense signal of active marrow on the background of bright fatty or aplastic marrow. These hypo-intense nodules could have been areas of residual normal marrow activity or due to partial response to steroid therapy (Figure 3b).

Discussion. The MRI appearance of bone marrow in T1-weighted images depends on the relative proportions of fat, water and trabecular bone.[3] T1-weighted images are chosen because they can easily differentiate between red functional marrow and yellow fatty marrow. In aplastic anemia there is an abundance of fatty or yellow marrow that replaces functional or red marrow and this gives the bone marrow a very characteristic appearance in T1-weighted images. The signal intensity of aplastic bone marrow in sagittal T1-weighted MR images of the spine is very bright, resembling that of subcutaneous fat and, in most cases, is not difficult to differentiate from normal age-related marrow changes.[6] Smith et al[7] studied the T1-weighted images of the lumbar spine in their study of 4 patients with aplastic anemia. They reported significantly lower T1 values compared to a control group. Olson et al[8] cautioned that in some cases of aplastic anemia these changes may not be distinguished from normal fatty bone marrow at other parts of the skeleton therefore MR imaging should always be correlated with trephine biopsy findings. The capacity of MR imaging to sample larger volumes of bone marrow spaces is a very useful adjuvant to, but not a replacement for, trephine biopsies. None of our patients had transfusion hemosiderosis, which can be a problem because it would tend to decrease the bone marrow signal and make it more difficult to recognize the presence of fatty marrow. Myelodysplastic syndromes may give a clinical picture similar to aplastic anemia but none of our patients had dysplastic features in peripheral blood smears or MRI patterns seen in MDS. Negendak et al[9] have shown that the detection of either focal or diffuse loss of the bright signal of aplastic fatty marrow, known as inhomogeneously cellular or diffusely cellular patterns, in the absence of hemosiderosis, may provide evidence of a clonal disease as myelodysplasia and may help in distinguishing between the 2 conditions. We present 3 cases where MR imaging was very useful in confirming the trephine biopsy findings and in the last 2 patients it also reduced the number of trephine biopsies needed to establish the diagnosis. The first of our patients died before referral for treatment could be arranged, while the other 2 were referred to another institution for treatment with anti-lymphocyte globulin (ALG) and therefore could not be followed-up by MR imaging. Follow-up with serial MR imaging in patients undergoing treatment for aplastic anemia may also be useful in detecting new foci of regenerating marrow suggesting response to therapy and thus reducing the need for multiple trephine biopsies.

We conclude that MR imaging is an accessible, non-invasive and widely available technique in Saudi hospitals, it allows sampling of large volumes of bone marrow tissue and is especially useful in the detection of fatty marrow replacement of the normal functional marrow in aplastic anemia.

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