

HUMORAL IMMUNODEFICIENCIES ASSOCIATED WITH BONE DYSPLASIAS

Adelle R. Atkinson, MD, FRCPC

Humoral immunodeficiencies represent approximately 50% of all immunodeficiencies.⁶ They range from complete absence of B cells and serum immunoglobulins (Bruton's agammaglobulinemia) to syndromes in which there are decreased (common variable immunodeficiency) or even normal (dysgammaglobulinemia) levels of immunoglobulins.

Throughout the last four decades there has been an increasing number of descriptions in the literature of immunodeficiencies associated with a variety of bone dysplasias. As early as 1965 McKusick et al¹⁵ described cartilage-hair hypoplasia, which was found to have an associated cell-mediated immunodeficiency. Other immunodeficiencies associated with bone dysplasias include adenosine deaminase deficiency (ADA), DiGeorge syndrome, Schimke immuno-osseous dysplasia, and short-limbed dwarfism (subclassified by immunodeficiency: combined, T cell, B cell).¹ The majority of these are T-cell or combined immunodeficiencies. This article focuses on novel syndromes of humoral and combined immunodeficiencies associated with bone dysplasias.

RELATIONSHIP BETWEEN THE IMMUNE SYSTEM AND THE SKELETAL SYSTEM

Given that a variety immunodeficiencies are associated with a variety of bone dysplasias, one wonders whether a developmental relation-

From the Division of Immunology and Allergy, Department of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

ship between these two systems exists; however, this relationship has yet to be elucidated.²⁰

Some interesting observations have been made using an athymic mouse model (*nu/nu*) and the so-called "motheaten mouse" (*me/me*).¹¹ The athymic mouse shows distinct abnormalities in T-cell maturation, whereas the motheaten mouse shows multiple defects especially with respect to B-cell differentiation. The splenic cells in the athymic mouse have been studied previously and were shown to have 2% mature T cells and a group of cells with incomplete T-cell features.¹¹ Studies of the bone from the tails of both of these mice models have shown distinctive abnormalities. The athymic mouse shows a decrease in bone turnover and formation. The formation of bone was found to be ten times lower than that seen in healthy littermates. Osteoclasts are less numerous and less active. In contrast, the motheaten model shows increased bone turnover. In vivo studies of both the nude and euthymic mouse strains have shown decreased vertebral tissue area and shorter tibia. The endosteal bone of the vertebrae showed decreased tetracycline labeling and reduced osteoclast index at 6 weeks of age.¹¹ The differences between the two distinct mouse models may indicate that the relationship between the cell-mediated and humoral components of the immune system and bone cells may in fact be quite different.¹¹

The microphthalmic mouse model (*mi*) offers yet more information about the relationship between bone formation and the immune system.²² This mouse possesses a 3-bp deletion of the *Mi* gene. This in turn alters the DNA binding site of the transcription factor gene product. A variety of mutations of the *Mi* gene exist resulting in various phenotypes. These phenotypes include small eyes, decreased eye pigmentation, deafness, lack of fur pigmentation, osteopetrosis, and decreased numbers of mast cells and natural killer (NK) cells. The $+ / mi$ and *mi/mi* genotypes specifically produce a phenotype of decreased number and function of mast cells, NK cells, basophils, osteoclasts, and macrophages.²² Examination of the bone marrow of these mice revealed that it had been altered in such a way as to preferentially exclude particular hemopoietic precursors. B-cell precursors were absent, and numbers of mature mast cells and NK cells were much lower when compared with the wild type. It has been postulated that these low numbers also can be attributed to decreased precursors in the bone marrow for these lineages.²² The physical bone marrow mass has been demonstrated to be more dense in the $+ / mi$ and *mi/mi* genotypes possibly due to decreased osteoclastic activity. This, however, cannot explain the absence of B-cell precursors. The authors hypothesize that the lack of these precursors may be due to an inhospitable cytokine environment.

Another interesting immuno-osseous model was developed by the knockout of the osteoprotegerin ligand (OPGL, also called RANKL).^{8, 22} These mice have severe osteopetrosis and lack osteoclasts. They also have an abnormal thymus structure and function, decreased number of B cells, and no lymph nodes. They have small body size, shortened limbs, abnormal teeth, and doming of the skull.⁸ Radiographs demon-

strate metaphyseal flaring with radiodense regions within the marrow cavity. Histology confirms osteopetrosis with disorganization of chondrocytes and lack of osteoclasts.⁸ RANKL has been shown to be an essential factor for osteoclastogenesis in the bone marrow. RANK thus appears to be essential for the development of both osteoclasts and lymph nodes and affects the differentiation of B cells.

This animal model and the *mi* animal both have decreased numbers of B cells and lack of osteoclastic activity. This suggests that osteopetrosis may somehow alter the bone marrow ultimately affecting B-cell development.²² Alternatively, *Mi* and RANK gene products may be essential for the process of B-cell development in addition to their role in osteogenesis.

Another theory for the origin of a defect that affects both immunologic and skeletal maturation stems from the PAX family of genes.¹⁹ This is a family of developmental control genes that encode nuclear transcription factors. PAX-5 for example codes for the transcription factor B-cell specific activator protein (BSAP). B-cell lymphopoiesis is dependent on this factor as illustrated by demonstration of an early block of B-cell development in mice lacking PAX-5. This is manifested by the absence of pre-B, B, and plasma cells.¹⁶ Another member of this gene family, PAX-3, is present in adult skeletal muscle,² and the so-called "splotch" (PAX-3 deficient) mouse shows embryonic defects of long-range cell migrations (e.g., somite to limb).²³ Given that there is developmental control over both skeletal and immunologic maturation within this family it is an area worthy of further investigation.

In humans, the genetic defect for spondyloepiphyseal dysplasia tarda has been localized to Xp22 in the approximately 2-Mb interval between DXS16 and DXS987.¹⁰ The phenotype present in these patients, however, does not include immunologic abnormalities. Patients with Roifman syndrome who have spondyloepiphyseal dysplasia as well as a humoral immunodeficiency have been shown not to have a mutation of this gene.^{14a}

HUMORAL IMMUNODEFICIENCIES AND BONE DYSPLASIAS

To date, only a small number of purely humoral immunodeficiencies associated with bone dysplasias have been described in humans (Table 1).

Antibody-Mediated Immunodeficiency with Short-Limbed Dwarfism

In 1974 Ammann et al¹ published one of the early descriptions of a purely humoral immunodeficiency associated with bone abnormalities. Two siblings were described who exhibited both clinical and laboratory

Table 1. HUMORAL IMMUNODEFICIENCIES ASSOCIATED WITH BONE DYSPLASIA

Clinical Syndrome	Inheritance	Immunologic Phenotype	Clinical Phenotype	Musculoskeletal Phenotype
Antibody-mediated immunodeficiency with short-limbed dwarfism (Ammann et al ¹⁾)	AR	Recurrent bacterial infections Low immunoglobulins Absence of plasma cells Negative PPD and candida skin test Negative IgE skin test Slightly decreased PHA response Abnormal ingestion and killing studies Reduced lymph tissue Hypoplastic lymph tissue Lymphadenopathy Hepatosplenomegaly Recurrent infections Normal immunoglobulin levels	Short stature Prominent nose High forehead Large ears	Shortened extremities Wide streaked metaphyses on radiographs Irregular ossification of femoral and tibial metaphyses
Roifman syndrome (Roifman ^{19, 20})	?X-linked	Poor/absent specific antibody levels Normal T-cell numbers, low B-cell numbers Normal T-cell proliferations Decreased B-cell proliferations	Male Premature (35-37 wk) IUGR Delayed gross developmental milestones Short stature Developmental delay Eczema Asthma Retinal changes—pigmentary changes, degeneration of the rod and cone system Dysmorphic features with prominent eyelashes, long philtrum and thin upper lip, narrow upturned nose, hypoplastic shallow midfacies and epicanthic folds, short tapered fingers and toes, hyperconvex nails, simian crease	Hypotonia Limitation in hip flexion Short stature Short hands and feet Clinodactyly of 5th finger Epiphyseal changes to vertebrae Changes to femoral head, condyle, tibia, and 3rd and 4th metacarpals

AR = autosomal recessive; PPD = purified protein derivative; PHA = photohemagglutinin

evidence of both short-limbed dwarfism and a humoral immunodeficiency.

Both of these children were noted to have short extremities, with height less than the third percentile, consistent with features of short-limbed dwarfism. Radiologically there was evidence of wide streaking of the metaphyses, with wide femoral metaphyses with irregular ossification of the femoral and tibial metaphyses.¹ Both of these children had recurrent bacterial infections including otitis media, sinopulmonary infections, pneumococcal meningitis, recurrent pneumonias, and pseudomonas infections. They had very low immunoglobulins and small but present lymphoid tissue. One of the children who was available for more in-depth testing demonstrated a negative purified protein derivative (PPD) and candida skin tests suggesting cellular immunodeficiency. This was further indicated by the slightly decreased phytohemagglutinin (PHA) response. In addition, abnormalities in ingestion and killing studies were demonstrated. An autopsy of one sibling showed hypoplastic lymphoid tissue, absence of plasma cells, and decreased numbers of lymphocytes. The thymus was present.¹

Along with this description Ammann et al took the opportunity to suggest a classification for patients who had the association of short-limbed dwarfism and immunodeficiency: Type 1: short-limbed dwarfism with combined antibody and cell-mediated immunodeficiency; type 2: short-limbed dwarfism with cell-mediated immunodeficiency (cartilage hair hypoplasia); and type 3: short-limbed dwarfism with antibody-mediated immunodeficiency. These patients were the first to enter the type 3 classification.¹

Antibody Deficiency, Growth Retardation, Spondyloepiphyseal Dysplasia, and Retinal Dystrophy: Roifman Syndrome

In 1997, Roifman²⁰ described a novel syndrome that included antibody deficiency, spondyloepiphyseal dysplasia, growth retardation, and retinal dystrophy in two brothers. In 1999 another publication described two more patients fitting the same phenotype who were unrelated and of different ethnic backgrounds.¹⁹

All of the patients described with Roifman syndrome were males born between 35 and 37 weeks' gestation with intrauterine growth retardation (IUGR). Gross motor milestones were delayed with sitting occurring between 8 and 12 months and walking between 3.5 and 4 years. Height was consistently below the third percentile in all patients. Head circumference was two standard deviations below the mean in two patients and in the third percentile in two patients.¹⁹

Cognitive development evaluated in three of the four patients showed borderline to mild developmental delay. Specific areas of deficiency included speech development, fine motor coordination, and math skills.¹⁹ Hypotonia was present in all patients during early childhood.

There was some limitation of hip flexion. These patients were short and had short hands and feet with clinodactyly of the fifth digit. Arm span was normal. Radiographic examination demonstrated abnormalities of the epiphyseal areas of the vertebrae as well as definite changes to the femoral head, femoral condyle and tibia, and the third and fourth metacarpals.¹⁹

Retinal abnormalities consisted of bilateral speckled pigmentary changes, abnormal angiography, and abnormal electroretinograms demonstrating widespread degeneration of the rod and cone system of the retina in two patients.¹⁹

All of the patients demonstrated dysmorphic features including long prominent eyelashes, down-slanting palpebral fissures, a long philtrum, and a thin upper lip. Clinodactyly of the fifth finger was also present in all patients, as were short tapered fingers and toes, a simian crease, and hyperconvex nails.¹⁹ Three of the patients had a narrow and upturned nose and two patients had hypoplastic shallow mid-facies and epicanthic folds. Recently, noncompaction of the ventricular myocardium (spongy myocardium) also has been described in association with Roifman syndrome.^{14a} This abnormality consists of excessive and prominent trabeculations and deep intratrabecular recesses within the ventricular wall. Hypogonadotrophic hypogonadism also has been described in association with Roifman syndrome by Robertson et al¹⁸ who describe a fifth patient with the clinical phenotype of Roifman syndrome. There appears to be no racial predisposition in this syndrome as all patients came from diverse backgrounds with no consanguinity. They have normal karyotypes and metabolic screens.¹⁹

Immunologically all of the initial patients had eczema and two had asthma. Most of the patients demonstrated a mild eosinophilia but a normal IgE. Infections in these patients included recurrent ear infections, pneumonias, sepsis, and recurrent herpes.¹⁹

All of the patients had lymphadenopathy and hepatosplenomegaly. Serum immunoglobulins showed normal IgG, normal IgA (except one patient whose was increased), and normal IgM in two patients and decreased in two patients. Isohemagglutinins (IgM) were low to absent in all patients. These patients did not mount a response to a polyvalent pneumococcal vaccine and furthermore did not show appropriate levels of antibodies to childhood vaccinations such as polio, tetanus, measles, mumps, and rubella even with re-vaccination.¹⁹

Flow cytometry showed normal numbers of T cells with normal ratios of CD4⁺ and CD8⁻ T lymphocytes. All patients showed normal proliferative responses to mitogenic stimulation for T cells but decreased for B cells. B-cell numbers were borderline low in all patients. When analyzed further it could also be demonstrated that the total number of antigen bearing B cells (sIg + B cells) was normal in most patients but the proportion was low. This suggested that between 20% and 50% of the B-lineage cells were immature. It was suggested that this may be due to a partial block of B-cell maturation.¹⁹

In vitro studies on these patients' B cells consisted of measuring

their response to ligation of the antigen receptor by anti-IgM. These cells clearly increased tyrosine phosphorylation on most substrates except the 70–72 kDA protein. This protein is the most strongly phosphorylated band and its identity is unknown. Interestingly, levels of Syk, Lyn, and Btk were normal in all patients. It has been hypothesized that the failure of these patients' B cells to respond to mitogenic stimulation may be related to a defect in signaling through the B-cell receptor (BCR). Given the multisystem involvement of this syndrome it has been further hypothesized that the gene responsible for this defect may belong to the PAX family, a family that consists of developmental control genes that encode nuclear transcription factors.¹⁹

PREDOMINANTLY CELL-MEDIATED IMMUNODEFICIENCIES AND BONE DYSPLASIA

T-cell immunodeficiencies along with combined immunodeficiencies are more commonly associated with bone dysplasia than humoral immunodeficiencies (Table 2).¹⁹ As the differential diagnosis of bone dysplasias must include all types of immunodeficiencies, an overview of these syndromes follows.

DiGeorge Syndrome

Hypocalcemic tetany, congenital heart disease, variable immunodeficiency, and unusual facies characterize DiGeorge syndrome.¹³ The thymus is absent or hypoplastic. These defects are secondary to a developmental abnormality of the third and fourth pharyngeal pouches. Many of these patients have the chromosomal abnormality of 22q11 deletions. These patients have a cell-mediated immunodeficiency, which varies in its clinical expression.¹³

Skeletal abnormalities associated with DiGeorge syndrome include micrognathia and aplasia of the mandible.¹¹ Temporal bone abnormalities also have been reported.¹⁷

Cartilage-Hair Hypoplasia

This syndrome has been commonly reported among the Amish peoples and has an autosomal recessive inheritance.¹⁵ The clinical phenotype, which is obvious at birth, is that of short-limbed dwarfism with short limbs, bulging forehead, "scooped" out nose, hyperlaxity of the joints, bowed legs, and a normal head.¹⁵ The patients' hair is fine and silky and their eyebrows and eyelashes are sparse. The associated immunodeficiency was initially suspected when some of these patients died from varicella infections and so-called "vaccinia."^{13, 15} Although the immunodeficiency is predominantly cell-mediated, it also can be combined

Table 2. CELL-MEDIATED IMMUNODEFICIENCIES ASSOCIATED WITH BONE DYSPLASIA

Clinical Syndrome	Inheritance	Immunologic Phenotype	Clinical Phenotype	Musculoskeletal Phenotype
DiGeorge syndrome	22q11	Thymic dysplasia or aplasia Cell-mediated immunodeficiency	Agnesis of parathyroid glands Hypocalcemia Congenital heart defect— interrupted aortic arch Renal abnormalities Hypertelorism, low-set ears, nasal cleft, shortened philtrum, cleft palate, choanal atresia, bifid uvula, high arched palate Hair—sparse, fine, silky Eyebrows and eyelashes sparse Hair breaks easily	Micrognathia Aplasia of the mandible Temporal bone abnormalities
Cartilage-hair hypoplasia (McKusick et al ¹⁵)	AR	Low T-cell numbers Decreased proliferations Lymphopenia Specific antibodies and immunoglobulins usually normal		Short limbs Bulging forehead Scooped out nose Loose joints Bowing of the legs Normal head
Schinke immuno- osseous dysplasia	AR	Overwhelming viral and opportunistic infections Decreased numbers of T cells especially CD4 ⁺ Decreased proliferation to mitogens May have low specific antibodies	Broad low nasal bridge with a bulbous nasal tip Protruding abdomen Abnormal hair Microdontia Ocular abnormalities Hyper-pigmented lesions IUGR Autoimmunity Renal disease Arteriosclerosis	Short stature Lumbar lordosis Flattened ovoid vertebrae Small and laterally displaced capital femoral epiphyses Dysplastic hips Epiphyseal changes Abnormal cartilage histologically

AR = autosomal recessive

with humoral deficiency.¹³ This syndrome is type 2 in Ammann's classification.¹

Verloes et al²⁴ in 1990 reported several cases of patients who were similar in phenotype to patients with cartilage-hair hypoplasia. The only difference was that their hair was normal. These patients had stunted growth with disproportionate limb shortening, short hands and feet, and normal face. The long bones were shortened with abnormalities of the metaphyses. The immune phenotype of these patients was not reported.²⁴

Schimke Immuno-osseous Dysplasia

This syndrome is an autosomal recessively inherited disorder, which has a number of distinctive features. It affects each sex equally and is widely spread geographically.³ These patients have a broad, low nasal bridge with bulbous nasal tip. They have short stature with lumbar lordosis and a protruding abdomen. Some patients have abnormal hair and microdontia as well as ocular abnormalities and hyperpigmented lesions. Their skeletal abnormalities include flattened ovoid vertebrae as well as small and laterally displaced capital femoral epiphyses. The hips are dysplastic. There are a variety of epiphyseal changes, which have been described. Histologic examination shows a lack of columnization of endochondral bone, nests of chondrocytes within resting cartilage, and decreased cellularity of resting cartilage.³ Many of these patients are born with IUGR and are normal intellectually and neurologically. Some patients have evidence of autoimmunity with anemia or thrombocytopenia. Renal disease in these patients is usually focal segmental glomerulosclerosis (FSGS) and is extremely difficult to manage. Arteriosclerosis is common and often results in cerebral infarcts or transient ischemic attacks. T-cell immunodeficiency is the predominant feature of the immune phenotype. T-cell subsets, CD4⁺, and CD3⁺/CD4⁺ cells are reduced, whereas CD8⁺ and CD3⁺/CD8⁺ are low or normal in some patients. Proliferation to mitogen stimulation is decreased. B-cell numbers and immunoglobulins may be normal, but some patients do demonstrate a deficiency in specific antibodies. These patients contract overwhelming viral and opportunistic infections in keeping with their immune phenotype.³

COMBINED IMMUNODEFICIENCIES WITH BONE DYSPLASIA

Adenosine Deaminase Deficiency

Adenosine deaminase deficiency (ADA) (Table 3) manifests as a form of severe combined immunodeficiency (SCID).¹² Deficiency of this enzyme of purine metabolism from the purine salvage pathway eventu-

Table 3. COMBINED IMMUNODEFICIENCY ASSOCIATED WITH BONE DYSPLASIA

Clinical Syndrome	Inheritance	Immunological Phenotype	Clinical Phenotype	Musculoskeletal Phenotype
ADA deficiency	AR, X-linked	Lymphopenic Recurrent infections Opportunistic infections, yeast Absence of lymph tissue Absence of thymic shadow on radiograph Low immunoglobulins Lack of specific antibodies Reduced numbers of T, B and NK cells Reduced/absent T- and B-cell proliferation	Failure to thrive May have liver disease	Cupping and flaring of rib ends on radiographs
Swiss-type agammaglobulinemia and achondroplasia (Davis')	AR	Overwhelming infection Absence of immunoglobulins No response to PHA Extremely small thymus Absence of lymphocytes Decreased lymph tissue Thymic dysplasia Decreased/absent immunoglobulins Abnormal PHA response Negative PPD and candida Absent isohemagglutinins Graft versus host disease Absence of plasma cells	Hypotonia	Shortened bowed extremities Normal head Small thorax Abnormal cartilage with delayed ossification Shortened extremities Short and wide pelvis Cupping of the radii Short stature
Combined immunodeficiency with short-limbed dwarfism and ectodermal dysplasia (Gatti et al')	?AR		Umbilical hernia Pectus excavatum Hypospadias Recurrent infections Absence of hair and eyebrows Eczematoid skin eruption	

Short stature/short limb skeletal dysplasia with severe combined immunodeficiency and bowing of the femora (MacDermot et al ¹⁹)	AR	Overwhelming infection Reduced T-cell numbers Decreased proliferations Reduced numbers of mature (CD20 ⁺) B cells	Short stature Shortened upper and lower limbs Bowing of the femora Abnormal costochondral junctions both grossly and microscopically Limb shortening Lumbar kyphosis Limitation of joint range of motion Radiographs demonstrated abnormal metaphyses and epiphyses in most bones Metaphyseal sclerosis of long bones and vertebrae
Spondylo-mesomelic-acrodysplasia with joint dislocations and severe combined immunodeficiency (Castriota-Scanderbeg et al ⁶)	AR	Overwhelming infection Thymus small and dysplastic T-cell proportions were very low as were immunoglobulin levels B-cell numbers were normal	Downward slanting palpebral fissures Long lashes Depressed nasal bridge Bulbous nasal tip Long philtrum Thin lips Short stature Autoimmune disease—ITP, thyroiditis
Combined immunodeficiency, autoimmunity and spondylometaphyseal dysplasia (Roifman and Costa ²¹)		Overwhelming infection Decreased numbers of T cells Decreased proliferations to mitogens and antigens Decreased specific antibodies Lymphadenopathy and hepatosplenomegaly	

AR = autosomal recessive.

ally leads to a build up of deoxyATP, which is toxic to lymphocytes.¹³ These patients present with marked failure to thrive, recurrent infections with opportunistic pathogens, recurrent diarrhea, extensive candidiasis, and laboratory evidence of a combined immunodeficiency.¹² They demonstrate a profound lymphocytopenia, absence of lymph tissue, and a thymic shadow. They have low immunoglobulins and low specific antibodies and fail to mount a proliferative in vitro response of lymphocytes to both mitogenic and antigenic stimulation. Associated with this immune phenotype is a growth abnormality of costochondral junctions causing cupping and flaring of the rib-ends.¹² There also may be abnormalities of both the scapulae and the transverse processes of the vertebrae.¹³ Although the treatment of choice for ADA deficiency is bone marrow transplantation from an HLA-identical sibling donor this may not always be possible. Enzyme replacement is an alternative for these patients¹² and its administration may be associated with reversal of the bony abnormalities.⁵

Swiss-Type Agammaglobulinemia Associated with Achondroplasia

Davis⁷ in 1966 presented a clinicopathologic conference that described a newborn female with achondroplasia and a combined immunodeficiency. This infant was found at birth to have the clinical features associated with achondroplasia including a small thorax and normal head with short bowed extremities. She was also hypotonic with a small thoracic cavity. The infant died at 9 weeks of age from overwhelming infection and was found to have agammaglobulinemia and no response in vitro to PHA. Her autopsy report showed an extremely small thymus ($\frac{1}{2}$ of normal weight), an absence of lymphocytes, and abnormal cartilage with delayed ossification.⁷

Combined Immunodeficiency with Short-Limbed Dwarfism and Ectodermal Dysplasia

Gatti et al⁹ in 1969 described two siblings, male and female, who presented at birth with agammaglobulinemia as well as evidence of cell-mediated immunodeficiency, short-limbed dwarfism, and ectodermal dysplasia. These children were born with obvious dysmorphic features. They both had evidence clinically and radiologically of shortened upper and lower limbs, shortened and widened pelvis, short ribs and cupping of the distal radii. These findings were consistent with a variety of short-limbed dwarfs. Both had recurrent and overwhelming infections to which they eventually succumbed. Most of these infections were bacterial in origin. The second sibling, who lived slightly longer than the first, also exhibited eczematoid skin changes and eventually lost all her hair. The first sibling had no hair or eyebrows. Both patients showed de-

creased but not absent lymphoid tissue. There were extremely low to absent immunoglobulins and the second sibling, who was more extensively investigated, showed no isohemagglutinins, decreased proliferation to PHA, and negative skin reactions to PPD and candida.⁹ Postmortem examination showed thymic dysplasia in both patients as well as abnormal infiltration of histiocytes and phagocytosis in multiple tissues of the first sibling. This child was also believed to have histologic evidence of graft versus host disease, which could have been secondary to a nonirradiated blood transfusion.⁹ There were no plasma cells present in the postmortem tissues. Both children had normal chromosomes.⁹

Short Stature/Short Limb Skeletal Dysplasia with Severe Combined Immunodeficiency and Bowing of the Femora

MacDermot et al¹⁴ reported two newborn females with combined immunodeficiency and skeletal dysplasia. This autosomal recessive condition consisted of shortening of the upper and lower limbs with bowing of the femora. Short stature resulted. Both patients had overwhelming infection and decreased amounts of lymphatic tissue. At autopsy both patients had a small dysplastic thymus and decreased T- and B-cell numbers.¹⁴ Histologic examination of the costochondral junction revealed gross irregularities and microscopically lack of alignment of cartilage cells into columns with a paucity of matrix column formation.¹⁴

Spondylo-Mesomelic-Acrodysplasia with Joint Dislocations and Severe Combined Immunodeficiency

Castriota-Scanderbeg et al⁴ in 1997 reported another case of immunodeficiency associated with bone dysplasia. This female infant demonstrated limb shortening, lumbar kyphosis, and limitation of joint range of motion. She had dysmorphic features including downward slanting palpebral fissures, long lashes, depressed nasal bridge, bulbous nasal tip, long philtrum, and thin lips. Radiographs demonstrated abnormal metaphyses and epiphyses in most bones. Immunologically the infant appeared phenotypically SCID-like and died at 3 months of age from overwhelming infection. The thymus was small and dysplastic. T-cell proportions were very low as were immunoglobulin levels; however, B-cell numbers were normal.⁴

Combined Immunodeficiency, Autoimmunity, and Spondylometaphyseal Dysplasia

Roifman and Costa²¹ recently described for the first time the association of combined immunodeficiency, metaphyseal dysplasia, and auto-

immune phenomenon. Three patients were described: an 18-year-old girl and her 3½-year-old brother as well as a 5-year-old unrelated boy. All the patients had life-threatening infections and on evaluation demonstrated decreased proliferations to both mitogen and antigen stimulation.²¹ Humoral immunity also was affected in that the patients had low specific antibodies. All three patients had evidence of an autoimmune phenomenon including idiopathic thrombocytopenic purpura, thyroiditis, and autoimmune pneumonia. The bone abnormality consisted of metaphyseal sclerosis of the long bones and the vertebrae.²¹ The authors postulate that the inheritance of this condition is most likely autosomal recessive.

References

1. Ammann AJ, Sutcliffe W, Millinchick E: Antibody-mediated immunodeficiency in short limbed dwarfism. *J Pediatr* 84:200–203, 1974
2. Barber TD, Barber MC, Cloutier TE, et al: PAX3 gene structure, alternative splicing and evolution. *Gene* 237:311–319, 1999
3. Boerkoel CF, O'Neill S, Andre JL, et al: Manifestations and treatment of Schimke immunosseous dysplasia: 14 new cases and a review of the literature. *Eur J Pediatr* 159:1–7, 2000
4. Castriota-Scanderbeg A, Mingarelli R, Caramia G, et al: Spondylo-mesomelic-acrodysplasia with joint dislocations and severe combined immunodeficiency: A newly recognized immunosseous dysplasia. *J Med Genet* 34:854–856, 1997
5. Chakravarti VS, Borns P, Lobell J, et al: Chondroosseous dysplasia in severe combined immunodeficiency due to adenosine deaminase deficiency (chondroosseous dysplasia in ADA deficiency scid). *Pediatr Radiol* 21:447–448, 1991
6. Conley ME, Stiehm ER: Immunodeficiency disorders: General considerations. In Stiehm ER (ed): *Immunologic Disorders in Infants and Children*. Philadelphia, W.B. Saunders, 1996, p 203
7. Davis J: A case of Swiss-type agammaglobulinemia and achondroplasia. *BMJ* 2:1371–1374, 1966
8. Dougall WC, Glaccum M, Charrier K, et al: RANK is essential for osteoclast and lymph node development. *Genes & Development* 13:2412–2424, 1999
9. Gatti RA, Platt N, Pomerance HH, et al: Hereditary lymphopenic agammaglobulinemia associated with a distinctive form of short-limbed dwarfism and ectodermal dysplasia. *J Pediatr* 75:675–684, 1969
10. Gedeon AK, Colley A, Jamieson R, et al: Identification of the gene (SEDL) causing X-linked spondyloepiphyseal dysplasia tarda. *Nature Genetics* 22:400–404, 1999
11. Gruber HE: Bone and the immune system. *Proc Soc Exp Biol Med* 197:219–225, 1991
12. Hershfield MS: Immunodeficiency caused by adenosine deaminase deficiency. *Immunology and Allergy Clinics of North America* 20:161–175, 2000
13. Hong R, Clement LT, Gatti RA, et al: Disorders of the T-cell System. In Stiehm ER (ed): *Immunologic Disorders in Infants and Children*. 1996, pp 339–408
14. MacDermot KD, Winter RM, Wigglesworth JS, et al: Short stature/short limb skeletal dysplasia with severe combined immunodeficiency and bowing of the femora: Report of two patients and review. *J Med Genet* 28:10–17, 1991
- 14a. Mandel K, Grunbaum E, Benson L: Noncompaction of the myocardium associated with Roifman syndrome. *Heart*, in press
15. McKusick VA, Eldridge R, Hostetler JA, et al: Dwarfism in Amish II cartilage-hair hypoplasia. *Bull Johns Hopkins Hosp* 116:285–326, 1965
16. Morrison AM, Nutt SL, Thevenin C, et al: Loss- and gain-of-function mutations reveal an important role of BSAP (Pax-5) at the start and end of B cell differentiation. *Semin Immunol* 10:133–142, 1998

17. Ohtani I, Schuknecht HF: Temporal bone pathology in DiGeorge's syndrome. *Ann Otol Rhinol Laryngol* 93:220-224, 1984
18. Robertson SP, Rodda C, Bankier A: Hypogonadotrophic hypogonadism in Roifman syndrome. *Clin Genet* 57:435-438, 2000
19. Roifman CM: Antibody deficiency, growth retardation, spondyloepiphyseal dysplasia and retinal dystrophy: A novel syndrome. *Clin Genet* 55:103-109, 1999
20. Roifman CM: Immunological aspects of a novel immunodeficiency syndrome that includes antibody deficiency with normal immunoglobulins, spondyloepiphyseal dysplasia, growth and developmental delay, and retinal dystrophy. *Canadian Journal of Allergy & Clinical Immunology* 2(3):94-98, 1997
21. Roifman CH, Costa T: A novel syndrome including combined immunodeficiency, autoimmunity, and spondylometaphyseal dysplasia. *Canadian Journal of Allergy & Clinical Immunology* 5:6-9, 2000
22. Roundy K, Kollhoff A, Eichwald EJ, et al: Microphthalmic mice display a B cell deficiency similar to that seen for mast and NK cells. *J Immunol* 163:6671-6678, 1999
23. Tajbakhsh S, Cossu G: Establishing myogenic identity during somatogenesis. *Curr Opin Genet Dev* 7:634-641, 1997
24. Verloes A, Pierard GE, Le Merrer M, et al: Recessive metaphyseal dysplasia without hypotrichosis: A syndrome clinically distinct from McKusick cartilage-hair hypoplasia. *J Med Genet* 27:693-696, 1990

Address reprint requests to

Adelle R. Atkinson, MD, FRCPC
Division of Immunology and Allergy
Hospital for Sick Children
555 University Avenue
Toronto, ON M5G 1X8
Canada

e-mail: adelle.atkinson@sickkids.on.ca