Emery-Dreifuss Muscular Dystrophy

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ABSTRACT

Emery-Dreifuss muscular dystrophy (EDMD) is the third most common X-linked muscular dystrophy. This disorder is characterized by childhood onset of early contractures, humeroperoneal muscle atrophy, and cardiac conduction abnormalities. Weakness is slowly progressive, but there is a broad spectrum of clinical severity. Patients and carriers are at risk of sudden death. Regular cardiac evaluation is mandatory to assess the risk of cardiac arrhythmias. Unique atrial pathology is seen at autopsy. The mutated gene in EDMD is localized to the long arm of the X chromosome. Mutations in the gene lead to abolished synthesis of the gene product, emerin. Emerin is localized to the nuclear membrane of skeletal, cardiac, and smooth muscle. The term Emery-Dreifuss syndrome describes patients who have the EDMD phenotype without X-linked inheritance. There is no treatment for the underlying disease, but early placement of pacemakers may be lifesaving.

Keywords: Emery-Dreifuss dystrophy, arrhythmia, contracture

HISTORY

In 1964, Dreifuss and Hogan1 described eight members of a large Virginia pedigree demonstrating X-linked recessive inheritance. Although these investigators believed that the clinical features of affected males could be confused with Duchenne muscular dystrophy, there were unusual features. The authors emphasized the low incidence of pseudohypertrophy and slow, benign progression of disease. In six of the eight patients, they described wasting and weakness of the biceps and triceps, with relative sparing of the deltoid. They proposed a broader term to encompass this family, "X-chromosomal muscular dystrophy." Becker (1955, 1957 1962) and Kiener (1955) also described benign form of X-linked muscular dystrophy.2-4 In 1986, Emery and Dreifuss5 re-examined the Virginia pedigree. In addition to previously described features, they noted early Achilles and elbow contractures. Four of the patients had cardiac involvement. They felt that these were important distin-
gulping features from the Becker type of muscular
dystrophy.

There have been several reviews since 1966,24-26 but
the core features of the disease have remained consist-
ent. The name given to this disease has changed from
"X-linked scapulopopliteal syndrome"27 to "X-linked
hemoprotein muscular disease"10 to "Emery-
Dreifuss muscular dystrophy" (EDMD).11 The term
"Emery-Dreifuss syndrome" has also been helpful.10,11
The syndromic designation emphasizes the unusual
phenotype, whether the patient in question has autosomal
dominant inheritance, a primary neurogenic cause, or
sporadic occurrence.

CLINICAL FEATURES

Emery-Dreifuss muscular dystrophy is the third most
common X-linked recessive dystrophy. Five features de-
define EDMD.2,3,4 The condition is a progressive myopathy
with (1) early contractures of the Achilles tendons,
elbows, and spine; (2) slowly progressive muscle wasting
and weakness with predominantly humeral (upper arm)
and peroneal (lower leg) distribution, bilateral and ap-
proximately symmetrical; (3) cardiac conduction defect
or other evidence of cardiomyopathy; (4) muscle biopsy
showing myopathic features or overt muscular dystrophy;
and (5) pedigree consistent with unequivocal X-linked
inheretance. The clinical features are summarized in Table 1.

Most patients have a normal birth and early develop-
ment. The earliest symptom is usually difficulty walking
or climbing stairs. Although all the patients in the original
Virginia pedigree developed gait impairment at around age
5, many patients are asymptomatic until the second or third
decade. In the early stages of disease, activities of daily liv-
ing are generally unaffected except for tasks that require
the use of the biceps or triceps, such as push-ups or chin-
ups. The distribution of muscle atrophy and weakness first
involves the biceps and triceps and, in some patients, it re-
mains an "upper extremity, heart, and contracture prob-
lem" with little lower extremity weakness. Most affected
patients show some inability to heel-walk because of the
combination of early Achilles' contractures and calf atro-
phy, rather than selective weakness of the anterior com-
partment of the leg. However, as the disease progresses,
there is more proximal atrophy and weakness in the shoul-
der and pelvic girdle muscles (scapulohumerospineous-
peroninal). Relative sparing of the deltoid produces a char-
acteristic appearance of a rounded shoulder with marked
humeral muscle wasting (Fig. 1A-C). Scapular muscle
wasting may produce scapular winging early in the course
of disease. Partial footdrop is common because of the calf
weakness and Achilles' contracture (Fig. 2).

Contractures develop in the first decade or early in
the second, before there is significant weakness. Early
ankle contractures prevent full arm extension and after 5-10
years may limit extension to 90 degrees. Early ankle
contractures produce toe walking, but calf pseudohyper-
trophy is not seen. Spinal contractures limit neck and
trunk flexion but, in most cases, do not cause significant
functional impairment until severe. The unusual spinal
contractures are interesting. There is no limitation of ex-
tension, most patients have no spine flexion at all, bend-
ing over only because of unimpeded hip flexion. In ran-
cases, only the lower or upper spine is affected.

Mild facial weakness has been reported in some pa-
tients,5,15,16 but it is never prominent. There is no impair-
ment of extracranial muscles. Distal upper extremity mus-
cles typically remain strong as the disease advances but,
in severe cases, forearm muscle weakness and wrist con-
tractures may develop.6 Mild hand weakness is also re-
ported as a rare finding early in the disease.5,15,16 The deep
tendon reflexes are usually absent or reduced throughout
the course. There are no sensory abnormalities. A wad-
dling gait with a steppage component is common. There is
no cognitive impairment associated with EDMD.

There is heterogeneity both within and between
families with EDMD. The spectrum of mild contrac-
tures, minimal muscle weakness and normal daily activi-
ties in some patients is contrasted by severe weakness
and wheelchair confinement in others (Fig. 3a,b). We
counsel patients that they can anticipate a slow progres-
sion of disease throughout their lifetime.

<table>
<thead>
<tr>
<th>Table 1. Key Features of Emery-Dreifuss Muscular Dystrophy</th>
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<td><strong>Clinical findings</strong></td>
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<tr>
<td>Early contractures (elbow, ankle, spine)</td>
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<td>Muscle atrophy and weakness (hemoprotein distribution)</td>
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<td>Slow progression to include proximal muscles</td>
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<td>Risk of sudden death from cardiac pathology (carriers are</td>
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<td>also at risk)</td>
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<td>Electrocardiogram</td>
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<td>Low-amplitude or absent P waves, variable degree of</td>
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<td>conduction block, atrial paroxysms</td>
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<td>Electromyogram</td>
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<td>Myopathic with occasional neuropathic features</td>
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<td>Serum CK</td>
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<td>Mildly elevated (&lt;10× normal)</td>
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<td>Muscle biopsy</td>
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<td>Non-specific myopathic change (dependent on stage of</td>
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<td>disease)</td>
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<td>Type II fiber atrophy is an inconsistent finding</td>
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<td>Genetics</td>
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<td>X-linked recessive inheritance, STA-gene (Xq28)</td>
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<td>Gene product is emerin (localized to nuclear membrane)</td>
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CARDIAC MANIFESTATIONS

Cardiac involvement has been noted in patients
with EDMD since the early descriptions.5 The typical
patient has manifestations around the same time that sig-
ificant weakness appears. Patients may complain of
palpitations or experience syncope as early signs of
arhythmia, but many are asymptomatic. Cardiac as-
sufflation is usually normal, but an irregular rhythm is
an early clue to pathology. The degree of cardiac involve-
ment does not correlate with the severity of weak-
ness.6,17 It is therefore important to investigate patients
Early in the course of disease, carriers are also at risk of cardiac arrhythmias and sudden death.\textsuperscript{18}

The earliest electrocardiographic (ECG) finding is low-amplitude or absent P waves and first-degree heart block.\textsuperscript{8} There is a gradual progression to second-degree and, finally, complete heart block.\textsuperscript{19} (Fig. 4). Bradycardia with a nodal rhythm, atrial fibrillation, and flutter appear as the heart block progresses.\textsuperscript{5,11,16} Ventricular arrhythmias and a four-chambered cardiomyopathy may eventually develop in advanced cases.\textsuperscript{5,9,10,20–22} Yoshioka et al.\textsuperscript{22} have documented tricuspid and mitral valve regurgitation, left ventricular hypokinesis, and perfusion defects. In 1992, Marshall and Huckell\textsuperscript{23} reported detailed electrophysiologic data in a patient with atrial paralyis, now recognized as a pathognomonic feature of EDMD. Their inability to pace the atria proved that the atrial myocardium was affected, rather than purely impaired impulse generation or transmission.\textsuperscript{23} Voit et al.\textsuperscript{16} have reported additional atrial and ventricular abnormalities: (1) supraventricular heterotopia, (2) ventricular heterotopia, (3) abnormal end-diastolic diameters, (4) myocardial hypertrophy, and (5) varying degrees of heart block and abnormal rhythms.

We have previously reported patients with marked variation in the evolution of cardiac manifestations.\textsuperscript{8} A patient with a normal ECG at age 16 had first-degree heart block with a normal rate at ages 40 and 43. Another patient had atrial fibrillation at age 28, but at age 52 had atrial fibrillation with tachycardia and wide QRS complexes. This finding is different from the usual progression to bradycardia and complete heart block, which is more typical of EDMD.\textsuperscript{24}

The potential complications of the cardiopathy include presyncope, syncope, cerebral and pulmonary emboli, congestive heart failure, cor pulmonale, and sudden death, which may occur in the early twenties, while the patient is fully functional. Carriers are also at risk. Fishbein et al.\textsuperscript{18} reported the sudden death of a 45-year-old carrier, attributable to a presumed arrhythmia, who had no other manifestations of the disease. She had a previously documented prolonged QT interval and intermittent junctional rhythm, but a normal echocardiogram. The tachycardia in this patient and two other males with EDMD showed loss of atrial muscle with fatty replacement, atrial fibrillation, ventricular fibrosis, conduction system fibrosis, left ventricular dilatation, and atrial mural thrombi in one patient.

Figure 1. 55-year-old patient with EDMD. (A) There is prominent humeroperoneal atrophy, relative sparing of the forearm muscles, and marked elbow contractures; (B) anterior view reveals the humeroperoneal atrophy with relative sparing of the deltoid muscles. Note the severe biceps atrophy. A pacemaker is located in the left anterosuperior chest; (C) the patient is unable to flex the lumbar and cervical spine due to severe contractures.
Figure 2. Foot drop and heel cord contractures in a 54 year old EDMD patient.

Figure 3. Lateral (A) and anterior (B) views of a 40-year-old EDMD patient with mild elbow contractures and minimal humeral muscle atrophy; (C) 54 year old EDMD patient who is wheelchair bound due to severe muscle weakness.
LABORATORY FINDINGS

CREATINE KINASE

The serum creatine kinase (CK) level is usually elevated. The degree of elevation is generally less than 10 times normal. The levels are highest in the early stages, gradually decreasing with age. Female carriers may also have mild CK elevation.

ELECTROPHYSIOLOGY

The findings of nerve conduction studies and electromyography (EMG) are influenced by the stage of disease and muscles chosen for study. The more severely affected muscles will logically have the more severe abnormalities. For example, the biceps and triceps may show marked abnormalities on needle examination, whereas the finger flexors may be normal. Nerve conduction studies in EDMD exhibit normal or decreased amplitude of the compound motor action potential (CMAP). A low amplitude of the CMAP occurs when recording from atrophic muscles. The motor conduction velocity is normal. The sensory nerve action potentials are normal. The findings on needle examination are predominantly myopathic, but neurogenic features are common. Insertional activity may be normal but is usually mildly increased with fibrillation potentials in affected muscles. The motor unit potentials (MUPs) are characterized by a mixture of short duration with low or high amplitude. In a 16-year-old boy, Cruz Martinez et al. used quantitative EMG and single-fiber EMG to show that the mean duration of motor unit potentials was decreased in the biceps, and the overall findings were consistent with myopathy. They noted increased fiber density and some MUPs with increased amplitude, but these findings do not equate with a primary neuropathic process. In fact, increased fiber density is common in other muscular dystrophies. Chronic myopathies frequently show increased amplitude in selected MUPs.

MUSCLE BIOPSY

There are no pathognomonic features of muscle biopsy in EDMD. Typical features reflect a nonspecific myopathic change. The spectrum of findings is broad and depends on the muscle chosen for biopsy. Typical findings in affected muscles, such as the biceps, include variation in fiber size, increased internal nuclei, occasional necrotic and regenerating muscle fibers, mild increase in connective tissue, and atrophic muscle fibers (Figs. 5, 6). Angular atrophic fibers, a typical neuropathic change, may be seen. The severe dystrophic features of Duchenne muscular dystrophy are not present. Although type I muscle fiber atrophy is a common feature of a prior series of patients, this change is not al-
ways present (Fig. 7). There have been reports of type I and II fiber predominance. Small groups of atrophic fibers may be the result of fiber splitting. A loss or decrease in type IIIB fibers has been reported by several investigators. The histopathologic features of the muscle biopsy are never diagnostic of EDMD, but merely serve as supportive of the diagnosis in the appropriate clinical setting.

**AUTOPSY**

In 1987, Harr et al. reported the autopsy findings in a 50-year-old man. They did not find abnormalities of the spinal cord, ventral roots, or anterior horn cells. Variable degrees of dystrophic change were seen in the muscles. There was a severe cardiomyopathy. The atria were enlarged with fatty replacement of nearly all of the atrial

(Figure 5. Trichrome stain of the quadriceps muscle biopsy from a 37-year-old EDMD patient. Note the variation in fiber size, atrophic muscle fibers, and many fibers with internal nuclei. Bar = 25 microns.

(Figure 6. H & E stain of the biceps muscle biopsy from a 20-year-old EDMD patient. Note the variation in fiber sizes, increased connective tissue (ct), hypertrophic (H) and atrophic (a) muscle fibers, fiber splitting (arrowhead), and a few regenerating fibers (arrow). Bar = 25 microns.)
Figure 7. ATPase stain (pH 9.4) of the quadriceps muscle biopsy from a 37 year old EDMD patient. Note that there is more Type 1 (lighter staining) than Type 2 (darker staining) fiber atrophy. Bar = 26 microns.

muscle. Ventricular abnormalities were less severe, but fibrosis of the ventricular septum produced bundle branch blocks. In 1992, Fishkin et al. reported the cardiac pathology in a female carrier and two affected males (Fig. 8). They found the same unique atrial pathology and nonspecific ventricular fibrosis. The conduction system was relatively well preserved compared with the severe changes in the atrial myocardium. One patient died despite placement of a pacemaker.

CARRIERS

Skeletal muscle weakness and contractures are rare in carrier females.12,30 Contractures are mild when present and rarely produce significant disability. The serum CK level is either normal or mildly elevated.2 EMG is performed in very few patients, but abnormalities are not expected in asymptomatic individuals. We now know that carriers of EDMD are at risk of sudden death.14 Cardiac arrhythmias may also develop.15,17,28,29 Six of 34 women in the original Virginia pedigree had arrhythmias. Their frequency of heart disease increased with age. The ECG may show low or absent P waves, with a variable degree of conduction block (Fig. 9). Atrial and ventricular arrhythmias must be considered whenever appropriate symptoms arise. We recommend annual ECGs for all female carriers. Holter monitoring is needed when investigating arrhythmias.

DIFFERENTIAL DIAGNOSIS

Recognizing the classical features of EDMD is not difficult, but several even more uncommon conditions can produce an appearance similar to that of EDMD.

The greatest difficulty has been with classification of patients with autosomal dominant inheritance whose condition cannot otherwise be distinguished from the X-linked form. In 1986, Becker proposed that the autosomal dominant form be named for the individual who first described this variation, Hauptmann and Thumlaesser,30,40 but this has not become a widely used term. Others have considered the term “Emery-Dreifuss syndrome” helpful because it calls attention to the risk of cardiac arrhythmias and sudden death in patients without X-linked inheritance.8,13

In 1985, Miller et al.32 reported a family with an affected daughter and father, who had many of the physical findings of the original EDMD patients.32 Both patients had atrial arrhythmias with heart block. An apical feature was enlarged calf muscles. These patient also had ventricular arrhythmias, which are more prominent in X-linked families. The serum CK was mildly elevated, and the EMG and muscle biopsy were myopathic. The daughter had hypoplastic and fused cervical vertebrae (C5-C6) of unknown cause. Finkel et al.34 described a family with a father and two affected children (son and daughter) with early onset of nonspecific weakness, atrial fibrillation with heart block, and variably degrees of contractures. The son’s EMG was neuropathy, but the muscle biopsy was myopathic. The father and daughter died of sudden death, but no autopsies were performed, and neither EMG nor biopsy results were reported.

A family with autosomal dominant inheritance and early progressive scapulopelvic muscle weakness with cardiomyopathy was described by Chakrabarti and Pearce.37 These investigators emphasized the difficulty in maintaining clinical distinctions for the scapulopelvic syndromes since this distribution of weakness can occur with neuropathic43-46 and myopathic47-50 etiologies. They also noted the problem of discordance be-
between the EMG and muscle biopsy as well as overlap of myopathic and neuropathic abnormalities in the same patient. Most of the original cases designated as "scapulopronal amyotrophy" had sensory loss. Davidenkov's syndrome is now used to describe patients with peripheral neuropathy and scapulopronal weakness.

The rigid spine syndrome (RSS) shares some of the features of EDMD: mild contractures of the elbows and ankles, spinal contractures that limit neck and trunk flexion, and childhood onset. Generalized muscle weakness in RSS is mild and generally nonprogressive. Although males are affected most frequently, the inheritance pattern is probably autosomal recessive or sporadic. The serum CK is normal or mildly elevated. The EMG is myopathic. The muscle biopsy features are of a nonspecific myopathic disorder: increased endomysial connective tissue, increased internal nuclei, necrotic muscle fibers, and variation in fiber size. Type I fiber atrophy has been reported, but others have not found selective involvement.

Bothlern myopathy is also distinguished from EDMD by lack of cardiac involvement. It is a slowly progressive myopathy with early contractures, usually affecting long finger flexors. There is a generalized distribution of muscle weakness, rather than selective humeropronal involvement.

Faciescapulohumeral muscular dystrophy (FSHD) is an autosomal dominant or sporadic disease. With full expression of disease, facial, scapular, and humeral dis-
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Figure 9. EKG from an asymptomatic 72-year-old female carrier of EDMD. Note the low amplitude P waves, first-degree heart block, and sinus bradycardia.

Distribution weakness develop. Peroneal weakness is also common. In patients with only mild facial weakness, the features that overlap with EDMD are more common. Early contractures, however, are not typical in FSHD. The age at onset of symptoms is generally later than in EDMD.62 Cardiac involvement is not a prominent feature of FSH, but P-wave abnormalities and infrautoconduction defects have been described.63 There are no documented cases of the atrial paralysis seen in EDMD. The serum CK level or EMG is unable to distinguish the two conditions. An inconsistent finding in muscle biopsy in FSHD is an inflammatory infiltrate,64 but the other myopathic features are similar to those in EDMD. Other familial or sporadic cases have been reported that resemble EDMD but either lack some of the characteristic features or have abnormalities not seen in EDMD.65

DIAGNOSIS

A definitive diagnosis of X-linked EDMD requires demonstration of a defect in the STA gene coding for emerin (see below). Monn et al.65 recently reported that the diagnosis can be made based on a skin biopsy demonstrating absent immunostaining of emerin in patients and diminished staining in carriers. They also found that peripheral blood cells could serve to identify patients but were unreliable for carrier detection. Those patients with an autosomal dominant history or sporadic cases with the EDMD phenotype have not had mutations identified in the emerin gene.76

TREATMENT

The disease has no effective treatment for the progressive weakness. Early contractures can be helped somewhat by physical therapy or surgical release. The use of orthotics is common, especially ankle-foot orthoses. All patients should be followed by a cardiologist who can assist in management of the cardiac manifestations. Because these patients are at risk of a very sudden death, cardiac pacemakers should be considered when P-wave abnormalities appear in an affected patient and certainly when the ventricular rate begins to fall. Evaluation with an annual ECG, Holter monitoring, or electrophysiologic studies may give life-saving early clues to cardiac disease. Unfortunately, patients have died with pacemakers in place from heart failure or secondary cerebral and pulmonary emboli, or they may have fatal ventricular arrhythmias. Antiplatelet or anticoagulant therapy is appropriate. Cardiac transplantation should be considered for patients without disabling weakness.12,77
Figure 10. Organization of the emerin (STA) gene in humans. Emerin maps to Xq28 within a 48-kb region shared with the Filamin gene which can be found normally and benignly inverted around two large repeats. The emerin gene itself is composed of 6 exons and 5 introns and is only 2.1 kb in length.

GENETICS

The gene responsible for EDMD maps to the distal band (Xq28) of the long arm of the X chromosome.76,77 The STA or emerin gene was identified as mutated in EDMD in 1994.80 This rather small gene is 2.1 kb in length and is composed of six exons.76 As shown in Figure 10, the emerin gene is located immediately distal to the Filamin gene (FLN1) within a 48-kb region flanked by two large (11.3-kb) inverted repeats.81 The orientation of the FLN1/emerin region is inverted on 18% of X chromosomes, presumably mediated by these repeats.82

Mutations of the emerin gene have been found in chromosomes of either orientation,83 and the repeats themselves may participate in deletions of the emerin locus leading to EDMD. Of 74 characterized mutations listed in the EDMD database (http://www.path.cam.ac.uk/edmd) or identified in the laboratory of one of the authors (STW), 34% are deletions ranging from a single nucleotide to 34 kb.84 Nearly 40% of the mutations are nonsense and result in truncated and usually absent protein whereas splice, insertion, and missense mutations compromise approximately 11%, 8%, and 6% respectively, of the defined mutations. Of these, nearly 90% result in the absence of emerin protein as judged by either Western blot analysis or immunohistochemistry. Thus, as an initial screen of males suspected of having EDMD, evaluation of emerin levels in peripheral blood will identify the vast majority of patients with X-linked EDMD.

The current protocol at Emory University School of Medicine calls for the initial evaluation for emerin mutations in males by first conducting western studies with monoclonal antibodies against emerin.85 Rather than using single-strand conformation polymorphism (SSCP) analysis advocated by others,86 we amplify the entire 2.4-kb emerin gene by polymerase chain reaction (PCR) and directly submit the product to automated sequence analysis. As shown in Figure 11, a previously unpublished case (patient 233) from Peru with typical presentation of EDMD at age 41 with progressive and generalized muscle weakness, contractures, and ventricular arrhythmia with auricular flutter shows the complex absence of emerin protein in peripheral blood lymphocytes. Subsequent automated sequence analysis of the emerin gene showed a novel 5-nucleotide insertion in exon 6, which would lead to a frameshift in the coding frame and the subsequent absence of emerin.

The emerin protein has a mass of 34 kD and has characteristics of membrane proteins of the secretory pathway involved in vesicular transport.87,88 The N-terminus contains a 40-amino acid domain similar to lamina-associated protein (LAP2) as well as C-hydrophobic domain. In addition, the protein is very serum rich, and recent evidence has demonstrated cell cycle-dependent protein phosphorylation.89 As predicted from the LAP2 similarity, emerin localizes to the inner nuclear membrane of skeletal, cardiac, and smooth muscles using immunofluorescence.85,90 In the absence of the C-terminus, emerin localizes to the nucleus, suggesting the presence of a nuclear localization signal elsewhere in the protein.91 However, in the heart emerin may also localize to the cellular membrane being found in interadhesive junctions, desmosomes, and fascia adherens.92 This observation would suggest that the absence of emerin in heart alters cardiomyocyte adhesion or possible communication between cells. Although this could account for the heart involvement, particularly arrhythmia, it remains unclear how the absence of emerin leads to skeletal muscle weakness. The identification of the mouse ortholog of emerin,92 which is 73% identical in amino acid sequence to human emerin, has allowed for currently ongoing studies to develop a knockout mouse model of EDMD that should prove valuable in answer-
Figure 11. Molecular diagnosis of patient 233 with the presentation of classic EDMD. (A) Western analysis of protein isolated from lymphocytes of normal and patient 233 probed with anti-emerin antibody. Note the absence of the normal 54 kDa emerin band in the patient lane. (B) Chromatography output from automated sequencing of a portion of exon 6 of the emerin gene. Note the 5 nucleotides insertion (boxed in the patient sequence) in the position noted by the arrow in the normal sequence.

ing these and other questions in addition to serving as a model for potential therapeutic interventions.

SUMMARY

Slowly progressive humeroperoneal weakness, early contractures, and cardiac arrhythmias characterize EDMD. The electrophysiology and muscle pathology usually indicate nonspecific myopathic change. Sudden death in patients and carriers warrants early cardiac evaluation and consideration of pacemaker placement. There is X-linked inheritance, but similar phenotypes may be autosomal dominant or recessive or may occur sporadically. How the absence of the gene product, emerin, produces skeletal muscle weakness remains to be determined.

REFERENCES

EMERY-DREIFUSS MUSCULAR DYSTROPHY—ZACHARIAS ET AL.


