A Case of Autoimmune-Related Retinopathy and Optic Neuropathy Syndrome Treated by Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation

Yu Oyama, MD, Richard K. Burt, MD, Charles Thirkill, PhD, Eissa Hanna, MD, Kevin Merrill, MD, and John Keltner, MD

Abstract: Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome is characterized by visual loss and often the presence of antibodies against retinal or optic nerve antigens in the absence of cancer. Limited success has been reported in treatment of ARRON syndrome with medications that suppress the immune system. In many patients, current strategies are insufficient to control the disease. A 47-year-old woman with progressive visual and hearing loss attributed to ARRON syndrome that was resistant to conventional therapies underwent autologous hematopoietic stem cell transplantation (HSCT). Clinical manifestations appeared to stabilize. This report suggests that autologous HSCT may have a therapeutic role in ARRON syndrome.

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In autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome, it is unclear whether antibodies against retina and optic nerve cause the visual loss or whether they represent an epiphenomenon related to nonspecific breakdown of retinal and optic nerve proteins or are part of the normal pattern of antibody distribution (1–8). For this reason, the condition is labeled "autoimmune-related" rather than "autoimmune."

Department of Medicine (YO, RKB), Division of Immunotherapy, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and Department of Ophthalmology and Vision Science (CT, EH, KM, JK), University of California, Davis, Davis, California.

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Address correspondence to John Keltner, MD, Department of Ophthalmology and Vision Science, Department of Neurology, and Department of Neurological Surgery, University of California, Davis, Davis, CA 95616; E-mail: jkeltner@ucdavis.edu

Several treatments based on standard therapy for autoimmune disorders have been tried in ARRON syndrome with variable success, including prednisone, intravenous methylprednisolone (IVMP), immunosuppressive agents, plasma exchange, and intravenous immunoglobulin (IVIg) (1,9–16). We describe what we believe to be the first reported patient to be treated with autologous HSCT.

CASE REPORT

In February 2001, a 47-year-old Caucasian woman presented for evaluation of visual loss. Her vision had deteriorated over the preceding 7 months with complaints of worsening glare from fluorescent lights, blurred vision in both eyes, and impaired night and color vision. She did not report photopsias. Her visual loss coincided with the onset of bilateral progressive hearing loss and episodes of high-pitched tinnitus. In addition, she described the sensation of "pins and needles" in her feet that over the next several months had evolved into bilateral lower extremity numbness and paresthesias. Over a 6-year follow-up, the patient developed bladder incontinence, disturbance in balance, and Sjögren syndrome (17).

In 1992, she had had *Mycoplasma* pneumonia and shortly thereafter chronic fatigue, polyarticular arthritis, and hypothyroidism with a thyroid biopsy yielding a benign nodule.

Family history included a malignant melanoma in an identical triplet sister, her brother, and a cousin. Neither of her triplet siblings had connective tissue disease.

In March 2001, our evaluation showed a visual acuity of 20/30-1 in the right eye and 20/25-1 in the left eye. Color vision tested on the American Optical Hardy-Rand-Rittler (AOHRR) plates was 2/6 in the right eye and 1/6 in the left eye (Note that the patient eventually lost color vision: 0/6 in both eyes on the AOHRR plates). Pupils were of normal size and reactivity without afferent defect. There was no evidence of inflammation in the eye.

Ophthalmoscopy demonstrated moderate optic disc pallor with attenuated blood vessels bilaterally.

Humphrey (stimulus size III) visual field examination showed further deterioration compared with an examination performed 1 month earlier. The mean deviation in the right eye had decreased from 9.1 to 13.38 dB with overall depression; the mean deviation in the left eye had decreased from 11.44 to 14.72 dB with a superior altitudinal defect.

Neuro-otologic examination demonstrated bilateral vestibular dysfunction with disruption of the vestibulo-ocular reflex and bilateral sensorineural hearing loss that proved to be progressive over the course of follow-up.

On neurologic examination, the patient exhibited decreased vibratory sensation in the toes and could not perform a tandem gait. Quantitative sensory studies and nerve biopsy, showing axonal and demyelinating changes, were consistent with a sensorimotor peripheral neuropathy. Brain MRI in January 2001 did not reveal any evidence of a demyelinating disease.

Additional studies with normal results included complete screening for heavy metals, human immunodeficiency virus, hepatitis, paraneoplastic disorders, serum homocysteine, and Lyme titer; immune electrophoresis; and SS-A/Ro, SS-B/La, rheumatoid factor (RF), antinuclear antibodies (ANA), antimicrosomal antibodies (AMA), anti-neutrophil cytoplasmic antibodies (ANCA), double-stranded DNA, anti-smooth muscle antibody (ASMA), fluorescent treponemal antibody absorption test (FTA-ABS), VDRL test, rapid plasma reagin (RPR) and microhemagglutination *Treponema pallidum* (MHA-TP), and vitamin B_{12}. Hematologic testing demonstrated macrocytosis.

Results of lumbar puncture, colonoscopy, chest CT, mammogram, dermatologic skin survey, and bone marrow biopsy were negative. On Western blotting, the patient's serum did not demonstrate any cancer-related retinal proteins. In the absence of malignancy, the patient's condition was considered most consistent with ARRON syndrome.

In April 2001, the patient began treatment with 20 mg prednisone three times daily (Fig. 1).

The patient's serum collected in December 2001 was evaluated for antibody activity against pig retina (Table 1A) and optic nerve (Table 1B). Specific regions of reactivity on the Western blot, designated by their respective molecular masses, were compared with the relative incidence of antibody activity of serum from 100 normal postmenopausal women volunteers as control serum. Table 1A reports the findings when the patient's sera and the sera of the normal control population were reacted against pig retina. Table 1B reports the results of reactions against pig optic nerve.

Despite prednisone treatment and other immunologic treatments outlined in Fig 1, the patient gradually lost vision. Optic disc pallor became profound. By March 2002, Humphrey visual fields could no longer be obtained, and Goldmann perimetry showed generalized constriction.

In September 2003, the patient was found to have very low counts of lymphocyte subsets compared with a normal lymphocyte phenotype done in 2001. Serologic testing for anti-heat shock protein (hsp)-70, associated with autoimmune inner ear disease, showed positive results. Antiphospholipid antibody (APA) IgM was elevated (14.9), consistent with a generalized autoimmune disorder.

In January 2004, the patient was referred to Northwestern University for evaluation of an autologous nonmyeloablative HSCT protocol approved by the institutional review board and Food and Drug Administration Investigational New Drug (IND) 11669. Hematopoietic stem cells (HSCs) were harvested. The immune ablative regimen was 200 mg/kg intravenous cyclophosphamide and 20 mg CAMPATH-1H.

In September 2004, unmanipulated autologous stem cells were infused. White blood cell and platelet counts recovered on day 10.

In March 2005, she reported increased energy, improved gait, vision, and hearing, as well as decreased spasms of the lower extremities and complete resolution of bladder dysfunction. Her chief complaints were extremity pain and photophobia and foreign body sensation in the eyes attributed to dryness.

In June 2005, audiometric testing showed a 5–10 dB improvement in pure tone threshold and a 10–15 dB improvement in speech reception threshold. Subsequent studies have demonstrated the patient's hearing to be stable.

In April 2006, serum was collected again and reevaluated for antibody activity against pig retina (Table 1A) and optic nerve (Table 1B). After HSCT, there was a reduction in the total number of antibodies against both target tissues. But there was also some new antibody activity. The significance of these changes is unknown.

In August 2006, ganzfeld electroretinography (ERG) and multifocal electroretinography (mfERG) showed slight improvement relative to results from July 2004. The pretransplant photopic B wave measured at 67.1 μVs right eye and 66.5 μVs left eye had improved to 75.4 μVs right eye and 88.9 μVs left eye (normal: 75.9–175.9 μVs). Similarly, the photopic flicker had improved from 62.0 μVs right eye and 57.1 μVs left eye to 72.0 μVs right eye and 77.8 μVs left eye (normal: 62.3–212.1 μVs). The scotopic B wave had improved from 400.6 μVs right eye and 376.5 μVs left eye to 458.5 μVs right eye and 468.9 μVs left eye (normal: 353.9–752.1 μVs). Although the right eye mfERG revealed no difference after treatment, the left eye mfERG demonstrated resolution of three of four points that were beyond 2 SDs from normal in the paracentral region.

In October 2006, visual acuity was 20/40 in both eyes with appreciation of the fly, 3/3 animals, and 5/9 circles

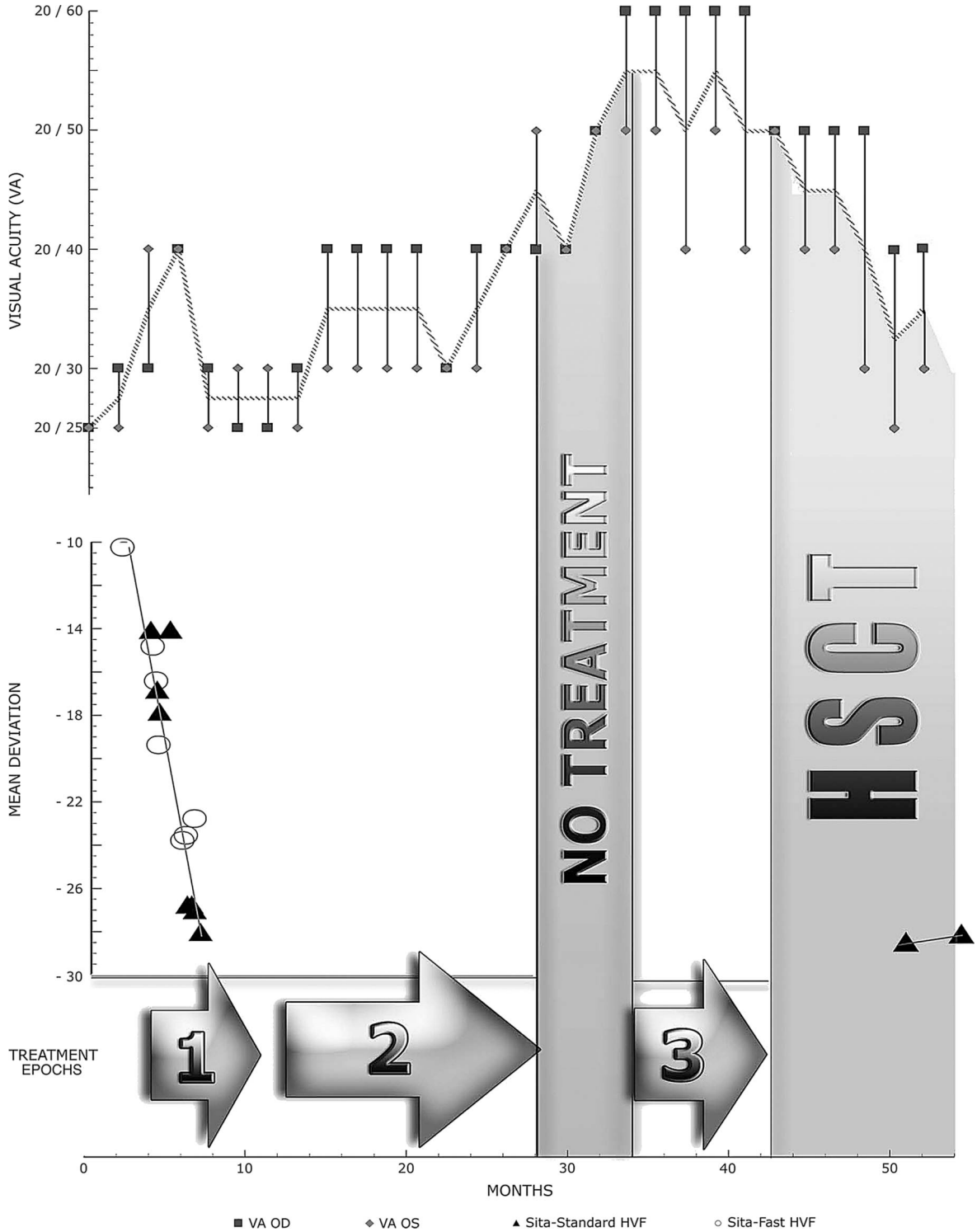

FIG. 1. Time course of patient's treatments and visual functional outcomes. Note that worsening of visual function occurred when the patient had discontinued intravenous immunoglobulin (IVIg) therapy and that improvement occurred after hematopoietic stem cell transplantation (HSCT). Key to treatment epochs: 1, April 2001: start 20 mg prednisone three times daily; May 2001: add methotrexate; June 2001: discontinue prednisone and methotrexate and start plasma exchange followed by IVIg and cyclophosphamide. 2, December 2001: start plasmapheresis followed by 0.4 g/kg IVIg monthly; August 2003: discontinue IVIg. Note acute worsening of visual acuity. 3, January 2004: resume monthly 0.4 g/kg IVIg; September 2004: perform HSCT.

TABLE 1. ***Our patient's antibody reactions against pig retina and optic nerve***

Antibody Activity Before HSCT, 12/12/01 (kDa)*	Relative Incidence of Antibody Activity in Control Group	Antibody Activity After HSCT, 4/26/06 (kDa)*	Relative Incidence of Antibody Activity in Control Group
A. Antibody Reactions Against Pig Retina			
26	5	26	5
30	36	47	1
38	3	55	8
42	1	72	12
48	2	96	7
55	8	104	11
71	8	148	0
96	7	NA	NA
103	16	NA	NA
107	5	NA	NA
B. Antibody Reactions Against Pig Optic Nerve			
31	1	39	0
35	2	81	0
39	0	119	0
47	5	NA	NA
86	4	NA	NA
128	3	NA	NA

HSCT, hematopoietic stem cell transplant. NA, not available.
*Molecular mass in kilodaltons of the antigen on retina or optic nerve that was found to be reactive with the patient's sera.

on Titmus stereo acuity testing. Color vision tested with AOHRR plates had improved from 0/6 to 2/6 in both eyes. Visual field improved to allow for recording with a Humphrey size V test object (Fig. 2) and has remained stable for 2 years since the transplant.

DISCUSSION

Because of the paucity of cases of ARRON syndrome, there is no reliable information on whether treatment is effective (1,9–16,18–32). The general approach consists of treating the underlying systemic disease if one is present. In the absence of a systemic disease, corticosteroids have been used first. Depending on the response to corticosteroid treatment, cyclophosphamide, methotrexate, IVIg, and plasmapheresis have been used singly or in combination.

In our patient, progressive hearing and visual loss was slowed by IVIg treatment (Fig. 1), whereas the peripheral symptoms continued to worsen. The non-myeloablative HSCT regimen used to treat this patient was selected because an identical regimen has been used safely and with promising results in systemic lupus erythematosus, other autoimmune diseases, and type I diabetes mellitus (33–37). In our patient, HSCT was well tolerated; there was an improvement in symptoms and a reversal of declining visual fields and acuity. There was also a reduction in the total number of antibodies after HSCT against both retina and optic nerve, but some new antibody activity was demonstrated. The significance of these phenomena is unknown.

The nosology of ARRON syndrome remains controversial. The first reports (18–23) of autoimmune optic neuropathy described patients with corticosteroid-responsive optic neuropathy, who had an idiopathic acute or subacute asymmetric loss of vision that improved after immunomodulation treatment. The available techniques did not allow detection of antibodies against retina and optic nerve. ERGs were not routinely used to evaluate retinal function. Later, patients with this condition were found to have antibodies to various layers of the retina and optic nerve (3,24–26). ERG abnormalities were frequently described and antibodies against recoverin (23 kDa) (24), Müller cells (25), a 22-kDa antigen (26), a 35-kDa antigen, and a 46-kDa antigen were eventually reported (6).

In 2004, the term autoimmune retinopathy (AR) was applied to patients who presented with paraneoplastic-like retinopathy in the absence of malignancy (6). All patients had ERG changes and nearly half had autoantibodies against retinal antigens. Other studies in patients with optic nerve dysfunction began to show a variety of autoimmune reactions to optic nerve and retina (1,7,26). In

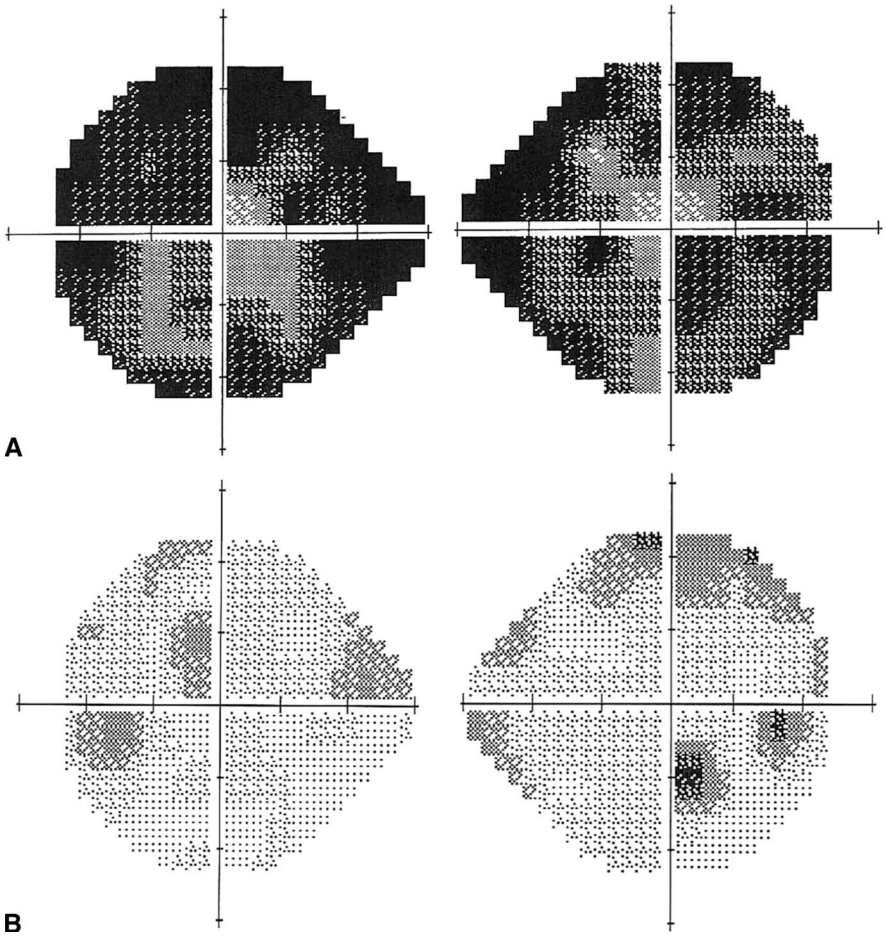

FIG. 2. Humphrey visual field size V gray scale results before hematopoietic stem cell transplantation (HSCT) in April 2002 (**A**) and 8 months after HSCT in May 2005 (**B**).

patients who did not show antibodies to retina or optic nerve, the absence of these antibodies has been attributed to impaired detection, individual sampling variation, or the immunosuppressed state of the patient undergoing treatment. The investigational challenge is further increased in the absence of a standardized control and method of study. To date, there are too few publications describing the prevalence of these antibodies in a large normal control group (27,38).

We agree with Shimazaki et al (27) that because antiretinal antibodies are present in a majority of normal control human sera, newly detected retinal autoantigens should be interpreted with caution and subject to rigorous testing for disease association. For this reason, we used 100 normal women as control subjects for our retina and optic nerve antibody determinations. Despite these normal control subjects, however, we do not know if the changes seen in our patient's serum represent more than an epiphenomenon (28).

We favor the term ARRON syndrome because it encompasses a disease spectrum that includes cases of retinal involvement, optic nerve involvement, and simultaneous retinal and optic nerve involvement. Table 2 is our attempt to define ARRON syndrome.

ARRON syndrome appears to be more common in women than men (2:1), with an average age of 50 years (range 37–75 years) (1,6). The visual loss is often asymmetric, with visual acuity varying from 20/20 to no light perception. ERG abnormalities are present in the majority of patients. In one report in which ophthalmoscopic findings were reported, 11 of 12 patients had optic disc pallor (1). In that report, nonspecific retinal changes were present in 8 of 12 patients (1). In the 58 patients for whom fundus findings were not reported, ERG abnormalities were found in all (6). In reports in which other clinical information is provided, 8 of 12 patients had other systemic autoimmune diseases (1).

The pathophysiology of autoimmune retinal and optic nerve degeneration in ARRON syndrome remains uncertain. Studies have demonstrated the specificity of anti-recoverin antibody, which stains photoreceptors, and

TABLE 2. ***Suggested diagnostic criteria for autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome***

All four of the following:
1. Visual loss as demonstrated either by visual acuity or visual field examination
2. No malignancy found after extensive evaluation*
3. Evidence of optic nerve or retinal abnormalities
4. No identifiable cause for optic neuropathy and/or retinopathy

One of the following:
1. Serum autoantibodies against retina and/or optic nerve not usually found in normal healthy individuals†
2. Response to immunomodulation demonstrated either by stabilization, slowing, or reversal of visual deficit

Modifiers:
Type A: Associated with other autoimmune disease
Type B: Not associated with other autoimmune disease

*Includes a history of remote malignancy that may better explain visual loss as being associated with cancer-associated retinopathy (CAR), paraneoplastic optic neuropathy (PON), and melanoma-associated retinopathy (MAR).
†The presence of autoantibodies to retina and/or optic nerve antigens does not prove causalilty.

anti-47-kDa antibodies, which stain ganglion cells, bipolar cells, and Müller cells (25,26,30). Other reports showed sera to have nonspecific retinal staining and optic nerve staining (1). Anti-hsp-70, anti–enolase, and anti-recoverin have all been shown to induce apoptotic retinal cell death (38–44). It is known that the infusion of antibodies against retinal elements, specifically S-antigen and recoverin, induces ERG changes in animal models (40). Adamus et al (5) have demonstrated that anti-recoverin antibodies induce an increase in intracellular calcium, leading to retinal cell death via a mitochondrial apoptotic pathway. In addition, nifedipine has been found to protect against anti-recoverin-induced apoptosis. (5) These studies imply a direct and specific role for autoantibodies in loss of visual function.

An extensive evaluation to rule out malignancy must be undertaken before the diagnosis of ARRON can be assigned. Patients with cancer-associated retinopathy (CAR), paraneoplastic optic neuropathy (PON), or melanoma-associated retinopathy (MAR) will often initially manifest visual dysfunction and only later be found to have a malignancy (29,45). Our recommendation for screening includes whole body imaging, bone marrow biopsy, dermatologic skin survey, colonoscopy, standard prostate screening, gynecologic examination, mammography, lumbar puncture, and serum testing for recoverin (29,45) and the 62-kDa neuronal antigen called collapsin response-mediating protein-5 (CRMP-5) (29,45,46).

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