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Nodal and extranodal plasmacytomas expressing immunoglobulin A: an indolent lymphoproliferative disorder with a low risk of clinical progression

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Abstract

Plasmacytomas expressing immunoglobulin A are rare and not well characterized. In this study, nine cases of IgA-positive plasmacytomas presenting in lymph node and three in extranodal sites were analyzed by morphology, immunohistochemistry, and PCR examination of immunoglobulin heavy and kappa light chain genes. Laboratory features were correlated with clinical findings. There were seven males and five females; age range was 10 to 66 years (median, 32 years). Six of the patients were younger than 30-years-old, five of whom had nodal disease. 67% (6/9) of the patients with nodal disease had evidence of immune system dysfunction, including human immunodeficiency virus (HIV) infection, T-cell deficiency, autoantibodies, arthritis, Sjögren's syndrome, and decreased B-cells. An IgA M-spike was detected in 6/11 cases, and the M-protein was nearly always less than 30 g/L. All patients had an indolent clinical course without progression to plasma cell myeloma. Histologically, IgA plasmacytomas showed an interfollicular or diffuse pattern of plasma cell infiltration. The plasma cells were generally of mature Marschalko type with little or mild pleomorphism and exclusive expression of monotypic IgA. There was an equal expression of kappa and lambda light chains (ratio 6:6). Clonality was demonstrated in 9 of 12 cases: by PCR in 7 cases, by cytogenetic analysis in 1 case, and by immunofixation in 1 case. Clonality did not correlate with pattern of lymph node infiltration. Our results suggest that IgA plasmacytomas may represent a distinct form of extramedullary plasmacytoma characterized by younger age at presentation, frequent lymph node involvement and low risk of progression to plasma cell myeloma.

Keywords

Extramedullary plasmacytoma; IgA; lymph node; plasma cell myeloma

Introduction

Extramedullary plasmacytomas (EMPs) are rare, typically solitary tumors comprising approximately 3–5% all plasma cell neoplasms.(42) Most present in middle-aged to elderly patients with a median age of 55-years-old at the time of diagnosis. EMPs are predominantly

localized to the head and neck regions, and are reported rarely in lymph nodes as a primary lesion. EMP often runs an indolent clinical course with a tendency for local recurrence, and progresses to plasma cell myeloma in about 15% of patients. (13,25) Only occasional cases of plasmacytoma expressing IgA (IgA plasmacytoma) have been reported in the literature,(3, 20,23,34) and the clinical and pathologic features of these tumors remain poorly defined. We identified an unusual index case of a young woman with multiply recurrent nodal IgA-expressing plasmacytomas first presenting at age 10. While the patient had multiple lymph node recurrences, progression to plasma cell myeloma was never observed during more than 20 years of follow-up. This case prompted us to undertake a study to better characterize IgA expressing plasmacytomas, and to contrast them with the features of IgG expressing plasmacytomas more commonly reported in the literature.(26)

Materials and Methods

Case selection

The consultation files of the Hematopathology Section of the National Cancer Institute, National Institutes of Health, Bethesda, MD, were surveyed for cases of extramedullary plasmacytoma. 12 cases expressing IgA were identified. One of these cases, Case 10, was previously reported.(46) IgA producing plasmacytomas were compared with 16 cases of extramedullary plasmacytoma expressing IgG collected over the same time period. This study was approved by the Institutional Review Board of the National Cancer Institute. Clinical information and follow-up were obtained from submitted patient records or referring physicians. Relevant clinical information was summarized in Table 1.

Histology and immunohistochemistry

Morphology and immunohistochemical features were studied on formalin-fixed and paraffin-embedded tissue sections. Immunohistochemical stains were performed using an automated immunostainer (Ventana Medical Systems, Inc. Tucson, AZ) according to the company's protocols, with minor modifications. Antigen retrieval was performed using a Tender Cooker (Nordicware, Minneapolis, MN) with citrate buffer. Antibodies included CD20 (L26, 1:1,000; Dako, Carpinteria, CA), CD79a (MB1, 1:400, Dako), Pax5 (24; 1:25; BD Transduction Laboratories), CD3 (F7.2.38, 1:50; Dako), CD19 (LE-CD19; 1:50; Dako), CD56 (1B6, 1:50; Novocastra), Cyclin D1 (SP4; 1:50; Neomarkers), CD138 (B-B4, 1:200, Dako), Kappa (1:25,000; Dako), Lambda (1:10,000; Dako), IgA (1:10,000; Dako), IgG (1:12,000; Dako), IgM (1:10,000; Dako), IgD (1:1,000; Dako), Ki-67 (Ki-67, 1: 100, Dako), Kaposi sarcoma-associated herpesvirus (KSHV/HHV-8) (LN53 ORF73, 1:2,000, Advance Biotechnologies Inc.). Positive and negative controls were performed with all cases and showed appropriate staining patterns.

In Situ Hybridization Studies for Epstein - Barr virus

In situ hybridization for Epstein-Barr Virus Encoded RNA (EBER) was performed on formalin fixed paraffin embedded tissue sections using a FITC labeled oligonucleotide probe (Ventana Medical Systems, Tucson, AZ) on an automated stainer (Ventana-Benchmark, Tucson AZ). Visualization was achieved using the ISH iView™ system with Alkaline-Phosphatase and NBT/BCIP substrate, with Fast red as contrast.

PCR Studies of IGH@ and IGG@ Gene Rearrangements

Genomic DNA was extracted from formalin-fixed and paraffin-embedded tissue sections using QIAamp DNA FFPE tissue kit (QIAGEN Inc. Valencia, CA) according to the manufacturer's instructions. For IGH@ clonality assays, PCR was performed on each sample using the framework 3 (VHα FRIII and JHα FRIII as reported by Segal et al. (39)) and framework 2

(FR2A as reported by Ramasamy et. al.(33) and JH α FRIII) consensus primers. A 50 μ l PCR reaction mixture contained about 0.2~0.5 μ g of DNA template in 1 $\times$ buffer II (Applied Biosystem, Foster City, CA) with 2.0 mM magnesium chloride, 0.25 mM each dNTP, 0.5 μ M of each primer, and 1.25 units of AmpliTaq Gold DNA polymerase (Applied Biosystem). For IGK@ clonality assays, PCR reaction using IGK@ Gene Clonality Assay for ABI Fluorescence Detection Kit (InVivoScribe Technologies) was performed according to the manufacturer's instructions. Briefly, 1 μ g of DNA template was mixed in 1 $\times$ IGK@ Tube A (or B) with 1.25 units of AmpliTaq Gold DNA polymerase (Applied Biosystem). The IGK@ primers were originally designed by BIOMED-2 concerted action BMH4-CT98-3936.(45) The DNA was amplified in a thermocycler (GeneAmp PCR System 9700, Applied Biosystems) for 7 minutes at 95°C followed by either 35 cycles (FRIII and IGK@ PCR reactions) or 40 cycles (FRII reaction) of amplification (95°C for 45 seconds; 60°C for 45 seconds; and 72°C for 90 seconds), and a final cycle of extension at 72°C for 10 minutes. After amplification, the PCR products were analyzed using ABI Genetic Analyzer 3130 (Applied Biosystem). The valid PCR product size ranges were 70~140 bp for IGH@ FRIII, 220~300 bp for IGH@ FRII, 120~160 bp, 190~210 bp, 260~300 bp for IGK@ Tube A, and 210~250 bp, 270~300 bp, and 350~390 bp for IGK@ Tube B. For IGH@ FRIII and FRII PCR, clonal rearrangement was defined as a single peak or double peaks with height $\geq$ 1000 florescent units and without a polyclonal background, or the height of the highest peak $\geq$ 2.5x of average of two neighbor peaks for normal distribution of bands; or the height of highest peak $\geq$ 1000 florescent units and $\geq$ 3x of the 3rd highest peak for skewed distribution of bands. For both IGK@ Tube A and B PCR, any peaks with height $\geq$ 2000 florescent units were considered indicative of a clonal rearrangement, except a peak at 147 and 196 bp in IGK@ Tube A, which is a recurring non-specific peak.(24,45) The combined analysis of IGH@ and IGK can identify about 85–90% of all clonal B-cell proliferations.

RESULTS

Clinical Findings

The clinical data are summarized in Table 1. There were seven males and five females with an age range at initial presentation from 10 to 66 years (median, 32 years). Six of the patients were younger than 30-years-old including 4 males and 2 females. Nine patients had nodal disease without extranodal involvement, and 7 of them presented with multiple regional lymph nodes or generalized lymphadenopathy. One patient (no. 8) had an incidental finding of plasmacytoma in dissected pelvic lymph nodes during surgery for endometrial carcinoma. Except for two patients (no. 5 with mild splenomegaly, and no. 9 with hepatosplenomegaly), all other patients showed no hepatosplenomegaly or constitutional symptoms such as fever, night sweats or weight loss. Three patients presented with extranodal disease, two involving the nasopharynx and one with a soft tissue mass. Of six patients who had bone marrow biopsies, five had negative bone marrow examination and one showed increased polyclonal plasma cells (24%) in the bone marrow (no. 4). Demographic features were compared with 17 extraosseous plasmacytomas expressing IgG. There were 10 males and 6 females; age range was 20–88 years (Median 54). There were nine nodal lesions and 8 extranodal, most of which involved nasopharyngeal or upper airway sites.

Immune system dysfunction was observed in 6 patients with nodal IgA-producing plasmacytomas, including one with HIV infection (no. 6), one with T-cell deficiency (no. 2), two with autoantibodies (nos. 3 and 5), one with Sjögren's syndrome, arthralgias, and hemolytic anemia (no. 9), and one with decreased CD19 positive B-cells and arthritis (no. 1). However, primary immune disorders such as Wiskott-Aldrich syndrome, common variable immunodeficiency, and autoimmune lymphoproliferative syndrome were not present in any patient. Immune system dysfunction was not observed in patients with extranodal

plasmacytomas. Most patients had no previous history of hematological malignancies with the exception of two patients, one with Burkitt lymphoma (no. 2); and one with small lymphocytic lymphoma in a cervical lymph node and myelodysplastic syndrome (no. 5). Both were treated and had no evidence of residual lymphoma at time of presentation with IgA plasmacytoma. Hypergammaglobulinemia was detected in 6 of 7 patients (86%) with nodal disease, and serum IgA was markedly elevated with absence of or only mild alterations of IgG or IgM levels. Serum protein electrophoresis and immunofixation studies (SPEP/IFIX) showed an IgA M-protein in 6 of the 7 patients, including the case without hypergammaglobulinemia (no. 3). Patient 1 had elevated IgA but no paraprotein. None of the patients with extranodal plasmacytomas had serum abnormalities (data available in 2/3).

Clinical follow-up was available in 7 patients, with a follow-up period following treatment ranging from 20 to 58 months (median, 34 months). Case No. 1 first presented with nodal disease at age 10, but was not treated until age 28 and remains in complete remission (CR) 48 months later following Rituximab. Two other patients were treated with Rituximab (nos. 2, 4), one of whom also received chemotherapy (no. 4). Case No. 2 was not responsive to monoclonal antibody therapy and had persistent but stable lymphadenopathy 31 months post diagnosis. Case No. 4 remains in CR. One patient with extranodal laryngeal disease received radiation therapy and remains in CR. Three patients (nos. 8, 11, 12) were not treated and remain asymptomatic and disease-free. Patient no. 9 is still in an early phase of treatment with chemotherapy.

Morphologic and immunohistochemical findings

Morphologically, the lymph nodes (#9) showed an infiltrate of plasma cells that was either interfollicular (nos. 1, 2, 3, 5 and 8) or diffusely effacing nodal architecture (nos. 4, 6, 7 and 9). The interfollicular pattern was characterized by a largely preserved architecture with or without marked follicular hyperplasia, and patent or dilated sinuses (Fig 1 and 2). The interfollicular/paracortical areas demonstrated sheets or aggregates of mature plasma cells; a focal paracortical nodular expansion of mature plasma cells was present in case 2. In lymph nodes with marked follicular hyperplasia (nos. 1, and 3), the lymphoid follicles were hyperplastic and the mantle zones were of normal thickness with polarization. Case 1 also showed some small atrophic lymphoid follicles, slightly increased vascularity between the lymphoid follicles and focally increased eosinophils. However, the mantle zones were not markedly thickened in the atrophic follicles and the interfollicular blood vessels were not hyalinized. The plasma cells were mature Marschalko type with little pleomorphism in two cases (nos. 1, and 5). The plasma cells in case 3 were largely immature with less condensed chromatin and higher N:C ratio (Fig 2D). Increased numbers of atypical forms with enlarged nuclei and bi- or multi-nucleation were present in two cases (nos. 2 and 8) (Fig 2B and 2F), and intranuclear pseudoinclusions (Dutcher bodies) and Russell bodies were readily identified. Mitotic figures were rarely found. The interfollicular plasma cells in all cases expressed IgA with immunoglobulin light chain restriction. In cases with marked follicular hyperplasia (nos. 1 and 3), small numbers of IgG-positive polyclonal plasma cells were identified in the germinal centers (Fig 1D, 1E and 1G).

Four cases (nos. 4, 6, 7 and 9) showed effacement of nodal architecture by a diffuse infiltrate of mature plasma cells. Only few scattered lymphoid follicles composed of small lymphocytes were seen (no. 9), sometimes only evident by immunohistochemical stains (Fig 3C). The plasma cells were mature with little atypia, rare intranuclear inclusions and rare mitotic figures.

Three cases presented with extranodal disease (nos. 10-12). One case with laryngeal involvement and one presenting as a soft tissue mass were composed of uniform sheets of mature plasma cells. Case 11, presenting in the nasopharynx, exhibited interfollicular infiltration by mature plasma cells with intervening reactive follicles.

Equal numbers of cases expressed kappa or lambda light chain ($6\kappa:6\lambda$). CD20 was negative in 11 of 12 cases, with focal expression seen in No. 3. The plasma cells were positive for CD138 and negative for CD56 and Cyclin D1 in all 12 cases. They were positive for CD19 in 6 of 9 cases tested (Table 2). In case 4, EBER showed small numbers of EBV positive cells in loose clusters that corresponded to CD20 positive B-cells. EBV RNA was not detected by EBER in the plasma cells or lymphocytes in other cases. Immunostains for human herpes virus type-8 (HHV-8) were negative in all cases.

Molecular genetic findings

Cytogenetic studies were performed in three patients (nos. 2, 3, and 5), and PCR analysis for immunoglobulin heavy chain (IGH@) and κ light chain (IGK) gene rearrangement was successful in 11 patients. One patient had a normal karyotype, while two had abnormal karyotypes, including t(14;15) and trisomy 1 (no. 2), and dup(1)(q21q31) (no. 3). Seven of 11 cases with successful PCR amplification (64 %) showed clonal IGH@ and/or IGK@ rearrangements, 60% (3/5) in cases with an interfollicular pattern of infiltration, and 66% (4/6) in cases with a diffuse plasma cell infiltrate. Four cases, two interfollicular (nos. 1 and 2) and two diffuse (no. 6 and 9), lacked definite evidence of a clonal population by IGH@ and IGK@ gene rearrangement, despite apparent light chain restriction by immunohistochemistry. Case 9 showed a peak highly suspicious for but not diagnostic of clonal IGH@ gene rearrangement in IGH@ FRII PCR reaction. These four patients had multiple sites of lymphadenopathy, and three were under the age of 30 years old. In patient 2 there was evidence of clonality by cytogenetic studies, suggesting that the normal PCR result for immunoglobulin gene rearrangement was a false-negative.

Discussion

In this study, we analyzed the clinicopathologic features of 12 cases of EMP with exclusive expression of IgA (referred to as IgA plasmacytoma in the discussion). Our study demonstrates that IgA plasmacytomas exhibit several distinctive features: (1) a high percentage of patients less than 30 years of age (6/12; 50%); (2) more common presentation in nodal, rather than extranodal sites (9/12; 75%) (3) frequent involvement of multiple lymph node sites, rather than solitary lesions; and (4) absence of progression to plasma cell myeloma in all patients herein reported.

Another notable feature was that 67% (6/9) patients with nodal IgA plasmacytomas (Nos. 1, 2, 3, 5, 6 and 9) had evidence of some immune system dysfunction such as arthritis, Sjögren's syndrome, autoantibodies with autoimmune phenomena, and T-cell deficiency including HIV-infection. Autoimmune diseases, such as Hashimoto's thyroiditis, Sjögren's syndrome, multiple sclerosis and the acquired immunodeficiency syndrome have been associated with expansion of monoclonal B-cells,(10,18,22,28,36) and even IgA-positive plasma cells.(48) Autoimmune diseases are at least partially mediated by abnormal T cell and/or T cell-dependent B cell responses against self-antigens, and it is well established that TGF- β produced by a subset of helper T-cells, known as Th3 cells, is essential for IgA production.(6,11,30) Therefore, there is a potential link between T-cell dysfunction, autoimmunity and IgA producing plasma cells. Given the benign clinical course of most IgA plasmacytomas, it is tempting to speculate that at least some of the cases represent exaggerated monotypic/monoclonal plasma cell proliferations related to dysregulated immune function, rather than an autonomous neoplastic proliferation. In contrast, plasma cell myeloma expressing IgA is a truly neoplastic process with some data indicating a more aggressive clinical course compared to that of plasma cell myeloma expressing IgG.(47)

A notable feature of IgA plasmacytoma was the low median age at presentation, 32 years, in contrast to a median age of 54 for our cases of IgG plasmacytoma. Similar to our data Menke

et al. identified a median age of 60 for their cases of nodal plasmacytoma, most of which expressed IgG.(26) In contrast, 6 of the patients with IgA plasmacytomas, five of whom presented with nodal lesions, were less than 30 years of age. Notably, plasma cell myeloma is a disease of middle-aged to elderly patients, and rarely occurs in adults under 30 years of age. (21,47) Moreover, IgA-producing myeloma is not usually associated with a younger age at presentation, with only 4.3% presenting below age 40.(47) However, there are multiple reports of IgA myeloma occurring in younger patients with autoimmune disease.(4,7,17,31,43) Some of these cases appear to overlap with IgA nodal plasmacytomas in having a low risk of lytic bone disease but generalized lymphadenopathy.(7)

Previous studies have identified monoclonal gammopathy in approximately 20% of EMPs. (15,40,41) In our study, monoclonal gammopathy was present in the majority of patients with nodal disease tested, but none of the patients with extranodal IgA plasmacytomas. Hypergammaglobulinemia with an IgA M-spike was identified in 86% patients (6/7), with one additional patient having an elevated IgA without an M-spike (no. 1). Of note, none of the patients had a serum M-protein over 30 g/L, except no. 4 with a serum IgA level of 82 g/L. The immunoglobulin light chain of the plasmacytoma always corresponded to that of serum immunoglobulin.

It is difficult to draw conclusions regarding the clinical outcome of IgA extramedullary plasmacytomas, given the heterogeneous therapies employed. However, all patients with available follow-up are alive, either with (1) or without (6) detectable disease. One recent case (No. 9) has only recently initiated therapy. None of the patients in our study showed progression to plasma cell myeloma.

PCR analysis demonstrated clonal IGH@ and/or IGK@ gene rearrangements in 64% (7/11) of cases with amplifiable DNA, supporting the clonal nature of plasma cell proliferation. The clonal nature of the plasma cells in case 4 was indirectly proven by the presence of monoclonal IgA M-spike detected by serum protein electrophoresis and immunofixation, but DNA was degraded and could not be amplified. One of the remaining PCR-negative cases had a clonal cytogenetic abnormality t(14;15) and trisomy 1 (no. 2). The abnormal cytogenetic findings, t(14;15) and dup(1)(q21q31) in patients 2 and 3, have not been described in plasmacytoma or plasma cell myeloma, and their clinical significance is unclear.

The diagnosis of IgA plasmacytoma was based on total or subtotal effacement by monoclonal plasma cells expressing IgA in lymph nodes or other extranodal site without evidence of bone marrow involvement. None of the patients had clinical or radiographic evidence of plasma cell myeloma. Partial vertebral compression fractures, rib fractures and distal tibia bone infarcts in patient 5 were felt clinically to be related to osteoporosis, and bone marrow exam was negative. Only one patient (no. 4) had significant plasmacytosis in the marrow. However, immunostains showed that the bone marrow plasma cells were polyclonal. Furthermore, the immunophenotypic features argued against a diagnosis of myeloma, as the plasma cells were generally positive for CD19 and negative for both CD56 and cyclin D1.

The differential diagnosis of nodal plasmacytoma includes marginal zone lymphoma (MZL) and lymphoplasmacytic lymphomas (LPL), both of which may have evidence of plasmacytic differentiation. (8,29,35,38,44) The distinction between plasmacytoma and MZL and LPL with extensive plasmacytoid differentiation is sometime problematic. Arguing against MZL and LPL was the absence of B-lymphocytes with plasmacytoid or monocytoid features, and absence of marginal zone expansion.(5) The atypical plasma cells lacked CD20, and in cases in which follicular hyperplasia was present, the plasma cells within the reactive follicles were negative for IgA and polytypic for kappa and lambda. It has been noted that extramedullary plasmacytoma in the head and neck region may progress to involve adjacent lymph nodes.(1,

12,19) However, the patients characterized as nodal plasmacytoma had no evidence of an extranodal mass lesion.

Histologically, IgA plasmacytomas had either an interfollicular or diffuse pattern of infiltration. No differences were observed according to the pattern of infiltration, either in clinical manifestations or clonality by genetic studies, although the number of cases is small. The plasma cells were mostly of mature Marschalko-type, corresponding to histologic grade 1 devised by Bartl et al for plasma cell myeloma,(2) with only one case showing more immature plasma cells (no. 3). In cases with an interfollicular plasma cell infiltrate, the combination of interfollicular plasmacytosis, follicular hyperplasia and increased paracortical vascularity may raise the possibility of the plasma cell variant of Castleman's disease (PC-CD).

Morphologically, PC-CD exhibits preserved follicles with either regressive features, or hyperplastic germinal centers in some cases, and sheets of interfollicular plasma cells.(16,32) The plasma cells in some PC-CD may be monoclonal, usually with lambda light chain restriction.(16,27,32) The majority expresses IgG and a small subset also expresses IgA.(16, 27,32) Only one case in our series (Case 1) had some follicles with regressive features, but there was no expansion of the mantle zones. In addition, the plasma cells were kappa light chain restricted.

The patients lacked the symptomatology (fever, night sweats and weight loss) or hepatosplenomegaly (with the exception of case 9) of multicentric Castleman's disease. In addition, all cases were negative for HHV8, including the patient with HIV infection (no. 6). Rare case reports of synchronous or metachronous plasmacytoma associated with multicentric Castleman's disease have been described.(9,14,37) However, none of our patients had a history suggestive of such a preexistent condition. Similarly, EBER was negative in all cases, with the exception of one case (no. 4) in which a small number of CD20-positive B-cells were positive; the plasma cells were negative for EBV.

In conclusion, extramedullary IgA plasmacytomas are associated with several distinctive features, including young age at presentation, low risk for progression to plasma cell myeloma, and association with autoimmune disease or immune dysfunction. Detailed clinical, laboratory and radiographic studies are necessary to rule out IgA producing myeloma for proper clinical management, especially in patients over 30 years of age.

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Figure 1.

Histopathology of IgA plasmacytoma with an interfollicular plasma cell infiltrate, case 1. The lymph node showed marked follicular hyperplasia with hyperplastic germinal centers, distinct and polarized mantle zones (A), moderate increase in vascularity in the paracortex, and heavy infiltrate of mature plasma cells in the interfollicular areas admixed with few small lymphocytes, immunoblasts and eosinophils (B, 200x). The interfollicular plasma cells showed κ light-chain restriction (C, D) and exclusive expression of IgA (E, F, G, H). Small numbers of polyclonal plasma cells expressing IgG were present in the germinal centers (C, D, E, F, G, and H, upper left corners).

Figure 2.

Histopathology of IgA plasmacytoma with interfollicular plasma cell infiltrate, cases 2, 3 and 8. Case 2 showed residual lymphoid aggregates with focal nodular expansion of plasma cells (A). Multinucleated plasma cells, Russell bodies and intranuclear cytoplasmic inclusions (inlet) were easily found (B, 400x). Case 3 showed follicular hyperplasia (C) and immature plasma cells with more open chromatin and higher N/C ratio (D, 400x). Case 8 showed markedly dilated sinuses with interfollicular and intrasinusoidal plasmacytosis (E). The plasma cells displayed significant pleomorphism with variation in size and shape, including some cells with markedly enlarged nuclei (F, 400x).

Figure 3.

Histopathology of IgA nodal plasmacytoma with a diffuse plasma cell infiltrate, case 6. The lymph node showed effacement of nodal architecture and diffuse infiltrate of mature plasma cells (A, and B, 400x), with κ light-chain restriction (D) and exclusive expression of IgA (E, F). Pax5 and IgD immunohistochemical stains highlighted residual aggregates of mantle cells that were not apparent on Hematoxylin and eosin stained sections (C).

Table 1
Summary of clinical features of 12 patients with IgA extramedullary plasmacytomas

Patient	Age (yr)/Sex	Clinical Presentation	Laboratory	Treatment and outcome (months)
1	10/F	Presented with painful and progressive left cervical adenopathy, up to 6–7 cm in size; Persistent left anterior cervical lymphadenopathy since age 8; Multiple lymph node biopsies at age 10, 15, 20 and 26 showed lymphoid hyperplasia; No hepatosplenomegaly; No constitutional symptoms; History of strep throat at age 8, hypothyroidism, Bipolar/Schizoaffective disorder, and arthritis.	CBC: normal; ↑IgA, normal IgG, ↓IgM, ↑IgE; SPEP/IFIX: no M-spike; ↑ESR, ↑CRP, ANA–, RF–	Treated with rituximab at age 28 with marked reduction of adenopathy (48 mos)
2	17/M	Presented with abdominal pain, nausea, vomiting and weight loss; Exploratory laparotomy showed small bowel obstruction by mesenteric and periaortic lymphadenopathy; No hepatosplenomegaly; No constitutional symptoms; History of Burkitt lymphoma in small bowel, status post surgery and chemotherapy, and in complete remission; History of T-cell deficiency by low CD4 counts and diminished mitogen stimulation proliferation assays.	CBC: mild anemia; ↑IgA, normal IgG, ↓IgM; SPEP/IFIX: IgA kappa M-spike; Bone Marrow: normal	Treated with rituximab and doxorubicin; Stable with persistent lymphadenopathy (31 mos.)
3	23/M	Presented with recurrent episodes of cervical, axillary, subpectoral, supraclavicular, and iliac/inguinal lymphadenopathy, up to 4.9 cm in size; No hepatosplenomegaly; History of autoimmunity including warm antibody-mediated hemolytic anemia.	No hypergammaglobulinemia; SPEP/IFIX: small IgG lambda M-spike one year ago, currently only IgA kappa M-spike; FC of node: normal	NA
4	17/M	Presented with neck mass, asthenia, anorexia, productive cough with hemoptysis and weight loss; No hepatosplenomegaly; No constitutional symptoms; CT scan showed bronchiectasis and generalized lymphadenopathy in cervical and submandibular areas, varied from 3 to 5 cm in size, and lymphadenopathy in multiple areas of mediastinum and upper abdomen; No bone lesions by skeletal survey.	CBC: anemia; ↑IgA, normal IgG, ↓IgM; SPEP/IFIX: IgA kappa M-spike; Negative serology for EBV, CMV, HIV, HCV, HTLV1 and toxoplasmosis; Bone Marrow: 24% polyclonal plasma cells.	Treated with CHOP with partial remission, most recent follow-up was nearly normal (normal CBC, slightly ↑IgA, and no adenopathy) (34 mos.)
5	65/F	Presented with fatigue; CT scan showed diffuse cervical, axillary, mediastinal, retroperitoneal and pelvic lymphadenopathy, up to 3.1 cm in size, and splenomegaly (14 cm); No constitutional symptoms; History of anemia with autoantibody to transferrin receptor (25 yr ago) treated with azathioprine and prednisone with good response, myelodysplastic syndrome (refractory anemia) with transfusion dependence, s/p horse antithymocyte globulin, small lymphocytic lymphoma in cervical lymph node, and s/p radiotherapy. Skeletal survey showed osteopenia, parial vertebral compression fractures, rib fractures and distal tibia bone infarcts.	CBC: anemia and leukopenia; ↑IgA, ↓IgG, ↑IgM (mild); SPEP/IFIX: IgA kappa M-spike; Bone Marrow: hypocellular marrow, 4% plasma cells.	NA

Patient	Age (yr)/Sex	Clinical Presentation	Laboratory	Treatment and outcome (months)
6	48/M	Presented with progressive mass in the midline of neck and diffuse lymphadenopathy; No hepatosplenomegaly; No constitutional symptoms; History of HIV infection on antiretroviral therapy.	CBC: leukopenia; CD4: 0.12k/ μ L	NA
7	66/M	NA; Right inguinal lymph node biopsy.	CBC: anemia	NA
8	52/F	s/p surgery for grade II uterine endometrioid adenocarcinoma, and bilateral selective lymphadenectomy; No adenopathy grossly.	CBC: normal; IgA, normal IgG and IgM; SPEP/IFIX: IgA lambda M-spoke.	No treatment, alive and asymptomatic (39 mos.)
9	20/M	Presented with massive systemic lymphadenopathy and hepatosplenomegaly; No constitutional symptoms; History of arthralgia, Sjogren's syndrome, and hemolytic anemia for 4 years	CBC: pancytopenia IgA, normal IgG, IgM; SPEP/IFIX: IgA kappa M-spoke. Bone Marrow: normal	Chemotherapy just initiated
10	16/F	Presented with progressive hoarseness and cough with sensation of foreign body in the throat; Laryngoscopy revealed a large granulation polyp overlying the right vocal cord; Magnetic resonance imaging (MRI) of the neck revealed a 7.6mm soft tissue mass involving the anterior right vocal cord; CT and PET scans were normal without lymphadenopathy or hepatosplenomegaly; No bone lesions by skeletal survey. (published, (41))	CBC: normal; SPEP/IFIX: normal; Serum immunoglobulins and β 2-microglobulin levels: normal; BM: normal with <1% plasma cells	Treated with radiation therapy; Remained asymptomatic (20 mos.)
11	37/M	Presented with a complaint of loud snoring becoming progressively worse; a 3 cm nasopharyngeal mass was found during corrective surgery	NA	No treatment; alive and asymptomatic (58 mos.)
12	54/F	Presented with soft tissue neck mass (3.8 cm); No hepatosplenomegaly; No constitutional symptoms; Bone survey was negative; CT scan showed no lymphadenopathy in chest, abdomen and pelvis.	CBC: normal; normal IgA, IgG, and IgM; SPEP/IFIX: no M-spoke; BM: normal, no plasmacytosis	No treatment; alive and asymptomatic (22 mos.)

M, male; F, female; ANA, antinuclear antibody; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SPEP/IFIX, serum protein electrophoresis and immunofixation; NA, not available

Table 2

Histologic, cytogenetic and molecular findings of IgA extramedullary plasmacytomas

Patient	Histologic findings	CD19	CD56	Cyclin D1	Light chain	Cyto-genetics	PCR	
							IgH	IgK
1	Preserved architecture; follicular hyperplasia with mixture of hyperplastic follicles and some small atrophic follicles; patent sinuses; interfollicular pattern of mature plasma cell infiltrate with monotypic IgA-expression; few polyclonal IgG intra-germinal center plasma cells.	w	-	-	κ	ND	p	p
2	Preserved architecture; few small atrophic follicles; dilated sinuses; IgA-expressing monotypic plasma cells in interfollicular areas with focal nodular expansion.	w	-	-	λ	t(14;15), trisomy 1	p	p
3	Preserved architecture; follicular hyperplasia with hyperplastic follicles; patent sinuses; paracortical expansion with IgA-expressing monotypic immature plasma cells	w	-	-	κ	dup(1)(q 21q31)	c	c
4	Partially effaced architecture; rare secondary follicles; patent sinuses; diffuse infiltrate of IgA-expressing monotypic mature plasma cells	ND	-	-	κ	ND	n	n
5	Preserved architecture; no lymphoid follicles; dilated sinuses; IgA-expressing monotypic mature plasma cells in paracortex and medulla.	w	-	-	κ	46, XX	c	c
6	Effaced architecture; diffuse infiltrate of IgA-expressing monotypic mature plasma cells.	ND	-	-	κ	ND	p	p
7	Effaced architecture; diffuse infiltrate of IgA-expressing monotypic mature plasma cells.	+	-	-	λ	ND	c	c
8	Preserved architecture; occasional lymphoid follicles; markedly dilated sinuses with sinus histiocytosis; IgA-expressing monotypic plasma cells in interfollicular areas, some with multinucleation or enlarged nuclei.	-	-	-	λ	ND	c	p
9	Largely effaced architecture; multiple scattered residual follicles; diffuse infiltrate of IgA-expressing monotypic plasma cells	ND	ND	-	κ	ND	s	p
10	Diffuse infiltrate of IgA-expressing monoclonal mature plasma cells.	+	-	-	λ	ND	c	c
11	Interfollicular infiltrate of IgA-expressing monoclonal mature plasma cells.	+	-	-	λ	ND	c	p
12	Diffuse infiltrate of IgA-expressing monoclonal mature plasma cells.	-	-	-	λ	ND	p	c

ND, not done; NA, not available; p, polyclonal pattern; c, clonal peak; κ, kappa light chain; λ, lambda light chain; n, no amplification product; s, suspicious for clonal gene rearrangement; w, weak.