Expect the Unexpected: Report of a Case of Pediatric Pharyngeal Extrasosseous Plasmacytoma with Tumefactive Amyloidosis (“Amyloidoma”) and a Review of the Literature

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Abstract We report a rare case of localized pharyngeal tumefactive amyloidosis caused by extrasosseous plasmacytoma in a 12 year-old girl who presented with otalgia, sore throat and blood stained sputum. The tumor was predominantly composed of amyloid with a limited component of well-differentiated neoplastic plasma cells, which were monoclonal (kappa restricted) on light chain in-situ hybridization. The amyloid deposits were positive for kappa immunoglobulin light chain on immunohistochemistry. The patient was treated with a combination of surgery and radiotherapy. Follow-up at 1 year showed no evidence of recurrence or progression.

Keywords Extrasosseous · Plasmacytoma · Amyloidosis · Pediatric · Plasma cell neoplasm

Background

Plasmacytoma (PC) represents 3–5 % of plasma cell neoplasms and is typified by a localized proliferation of monoclonal plasma cells. PC may be classified as either solitary PC of bone or extrasosseous plasmacytoma (EOPC) depending on whether it is intra- or extrasosseous. Plasmacytoma most commonly affects middle aged to older adult males [1]. As with all plasma cell neoplasms, EOPC is frequently associated with a production of an abnormal/monoclonal immunoglobulin (Ig), either as a complete Ig, or parts thereof, e.g. (monoclonal) light- or heavy chains, which may be detected in the blood, urine or

deposited in various tissues, sometimes as amyloid. EOPC affecting children/ adolescents is extremely uncommon, with most of the cases affecting the upper aero-digestive tract [2–8]. We herein present an unusual case of tumefactive localized amyloidosis in the pharynx, which was caused by EOPC in a 12 year-old girl.

Case Report

A 12 year-old girl with no significant past medical history or evidence of immunosuppression presented with right sided otalgia, sore throat and blood stained sputum of 2 weeks duration. The clinical examination revealed an exophytic right lateral pharyngeal wall mass that extended superiorly to involve the right Eustachian cushion. There was no lymphadenopathy. A biopsy of the mass under general anesthesia was performed. Following the histopathology report of the biopsy, an extensive workup was performed. A full blood count was normal. There was no evidence of hypercalcemia or renal failure. No M protein was detected on serum and urine protein electrophoresis. The human immunodeficiency virus (HIV) status was negative. Magnetic resonance imaging (MRI) showed a $37 \times 25 \times 18$ mm T1 weighted hypointense and mildly T2 weighted hyperintense-enhancing mass involving the right nasopharynx and obstructing the opening of the Eustachian tube (Fig. 1a). No intra- or extrasosseous lesions were identified on full skeletal X-ray examination as well as on MRI scans. A bone marrow biopsy showed a normocellular marrow, with trilineage hematopoiesis and no increase in plasma cells. Subsequently, the patient underwent surgical debulking of the pharyngeal tumor (with positive margins) followed by adjuvant radiotherapy. At

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Fig. 1 **a** MRI T2 weighted image showing a well demarcated mass in the right nasopharynx (red arrow). **b** Histologic examination showed several polypoid fragments containing abundant eosinophilic material. **c** Aggregates of mature plasma cells were present, in part

surrounding small glands. **d** The eosinophilic amorphous material showed apple green birefringence with congo red stain when microscopically examined under polarized light

1-year follow-up, the patient is well with no evidence of recurrence.

Materials and Methods

The specimen was fixed in formalin and embedded in paraffin. 4 µm thin sections were cut and stained with hematoxylin and eosin (H&E). An immunohistochemical study was performed using commercially available antibodies against CD56 (Clone 1B6, Novocastra, dilution 1:50), CD20 (clone L26, DAKO, dilution 1:1500), CD3 (Rabbit polyclonal, DAKO, dilution 1:100), kappa and lambda light chain (Rabbit polyclonal, DAKO, ready-to-use) and cyclinD1 (clone SP-4, Thermo scientific, dilution 1:20) according to the manufacturer's instructions. In-situ hybridization assays (ISH) for Epstein-Barr virus (EBV)-encoded small RNAs [EBER] (Leica Bond, ready-to-use) and kappa and lambda light chains (Leica Bond, ready-to-use) were also performed as well as special stain for Congo red (CR) dye.

Fluorescent in-situ hybridization (FISH) studies were performed on fresh tissue using dual fusion DNA probes (Abbott Molecular, USA) to detect translocations and gene fusions involving the heavy chain locus of immunoglobulin

gene (*IGH*) with fibroblast growth factor receptor 3 (*FGFR3/IGH*) t(4,14), cyclin D1 (*CCND1/IGH*) t(11,14) and V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene (*IGH/MAF*) t(14,16).

Results

Histopathology

Sections showed several polypoid pieces of mucosa diffusely effaced by eosinophilic material with some inflammatory cellular infiltrate (Fig. 1b). Higher magnification revealed mature plasma cells and abundant eosinophilic, amorphous extracellular material with scattered crack artifacts in the background, pushing the mucous glands apart (Fig. 1c). No Dutcher bodies were seen. No lymphoepithelial lesions or abnormal lymphoid population were identified. The CR-stain showed apple green birefringence of the homogeneous eosinophilic material under polarized microscopic examination, consistent with amyloid (Fig. 1d). The amyloid made up more than 95 % of the tumor volume. Focally, amyloid deposition was also identified within the walls of some blood vessels.

Special Studies

The plasma cells showed kappa restriction by ISH (Fig. 2a, b). The amyloid was positive for kappa and negative for lambda on immunohistochemistry (Fig. 2c, d). The limited number of plasma cells outside the amyloid deposits were polytypic for light chains on ISH. Very focally, there was co-expression of CD56 and CD20 in the plasma cells within the amyloid. Scattered CD3-positive T-lymphocytes were present. No immunoexpression of the plasma cells for cyclin D1 or nuclear positivity for EBV by ISH was present.

FISH analysis was negative for translocations involving *FGFR3*, *CCND1*, *MAF* and *IGH*.

Discussion

Plasma cell neoplasms affecting pediatric patients are distinctly uncommon. As in adults, EOPC predominantly occur in the upper aerodigestive tract [2–8]. Rare locations such as lymph node and gastrointestinal tract involvement have also been documented [9, 10]. Even more unusual is the occurrence of EOPC in conjunction with a large amount of light chain-amyloid (tumefactive amyloidosis—“amyloidoma”), which potentially may mask the presence of underlying, limited and mature—well differentiated,

albeit neoplastic plasma cells. We herein present such a case affecting a previously healthy 12 year-old girl. We have only been able to identify few cases similar to the case presented herein, i.e. EOPC in conjunction with amyloid in the pediatric age group, in the English literature [2, 3, 7, 8]. The cases are summarized in Table 1. Saad et al reported that the most common sites of presentation of laryngeal PCs in decreasing order of frequency are the epiglottis, vocal cords, ventricular bands, the arytenoids and the subglottic space [11].

From a differential diagnostic point of view, when encountering a polypoid hypocellular lesion such as our case, especially when it is associated with an eosinophilic background, it may be mistaken for a chronic inflammatory polyp with extensive stromal hyalinosis. This risk of missing the underlying plasma cell neoplasm is especially high in the pediatric age group where the suspicion for a plasma cell neoplasm is low. In fact, in the case reported by Nagasaka et al [7], the tumor was biopsied on two separate occasions, which revealed only amyloidosis with no evidence of malignancy. It was only in the subsequent excision specimen that EOPC was diagnosed. This case further emphasizes the importance of having a high degree of awareness of the possibility of an underlying plasma cell neoplasm when a localized accumulation of amyloid is encountered in pediatric patients.

Fig. 2 **a** The plasma cells showed kappa light chain restriction by in-situ hybridization. **b** There was no reactivity for lambda. The amyloid protein was positive for kappa light chain by immunohistochemistry (**c**, Kappa; **d**, Lambda)

Table 1 Summary of cases of pediatric/ adolescent EOPC with amyloid deposition in the head and neck

Case reports	Age	Gender	Site	Symptom(s)	Size	Methods of clonality	Rx	F/up
Current case	12	Girl	Pharynx	Otalgia, sorethroat, blood-stained sputum	3.7 cm	ISH	Es, RT	1 y
Rutherford et al. [2]	13	Girl	NPX SGT	Dysphonia	N/A	IHC	RT	N/A
Naples et al. [3]	17	Girl	SGT	Raspy voice, straining of speech	1.2 cm	IHC	Es, RT	2 y
Nagasaka et al. [7]	12	Girl	SGT	Hoarseness of voice	3 cm	IHC, ISH, molecular	Es, RT	4 y
Gonzales et al. [8]	11	Boy	Glottis	Dysphonia	N/A	IHC, molecular	Es, RT	3 y

Rx treatment, F/up follow up, ISH in-situ hybridization, Es excised, RT radiotherapy, y year(s), NPX nasopharynx, SGT subglottis, N/A not available, IHC immunohistochemistry

When faced with a neoplastic lesion that contains a monoclonal cell population with distinctive plasmacytic differentiation, the differential diagnoses that should be considered include plasma cell neoplasms, such as plasma cell myeloma and PC, and a spectrum of B cell lymphomas with plasmacytic differentiation such as extranodal marginal zone lymphoma (MZL) and lymphoplasmacytic lymphoma (LPL). Plasma cell myeloma is characterized by bone marrow-based, multifocal plasma cell neoplasm with a monoclonal protein in serum or urine, frequently associated with organ or tissue impairment/destruction. None of these were present in our patient. Although EOPC cannot be distinguished from extramedullary myelomatous involvement based on morphologic basis alone, the latter is frequently CD56 positive and not infrequently cyclinD1 and p53 positive, while EOPC is rarely positive for these markers [12]. However, taking into account not only the significant differences in presentation and clinical course, but also the different spectrum of chromosomal partners of 14q32 and consistent absence of the t(11;14) in EOPC, indicate that EOPC and plasma cell myeloma are different disease entities and not just different tissue manifestations of the same neoplastic process [13]. MZL and LPL are small B-cell neoplasms with a variably prominent plasmacytoid/plasmacytic component. The distinction between neoplastic cells with plasmacytic differentiation in mature B-cell lymphomas versus neoplastic plasma cells in bona fide plasma cell neoplasms is particularly difficult. Seegmiller et al found that plasmacytoid cells in lymphoma are more likely to express CD19, CD45 and surface Ig and less likely to express CD56 than those in myeloma [14]. In addition, their paper also addressed that some EOPC show a lymphoma-like phenotype, suggesting that, in reality, they may represent non-Hodgkin lymphomas with extensive plasmacytic differentiation. This could possibly explain the focal aberrant expression for CD20 in our case. In the paper by Bink et al, they also showed that there is absence of breaks involving the *MALT1* and *FOXPI* loci in EOPC, which are frequently involved in MALT lymphoma [13]. Interestingly, cases of MZL with amyloid deposition have been reported [15].

PC refers to a localized neoplastic proliferation of plasma cells, which can be intra- or extraosseous, in the absence of systemic involvement. The diagnosis of PC is based on recognition of plasma cells, which is fundamentally histological, coupled with immunohistochemical and/or other studies to establish monoclonality and correlation with clinicoradiological findings to exclude systemic involvement. There is no absolute number cut off criteria to diagnose a plasma cell neoplasm outside the bone marrow, as long as monoclonality is demonstrated. Rare cases of multiple synchronous EOPC involving several vicinity locations, e.g. nasopharynx and larynx, larynx and parapharyngeal space have been reported [2, 16, 17]. In this setting, it is of utmost significance to exclude bone marrow involvement. In the current case, albeit containing a very limited amount of neoplastic cells, kappa light chain restriction confirmed the monoclonal nature of the plasma cells. Although there was focal positivity for CD56, the absence of systemic involvement, negativity for cyclin D1 by immunocytochemistry, and absence of genetic abnormalities (gene rearrangements) reported in plasma cell myeloma, involving *IGH*, *CCND1*, *MAF* and *FGFR1* support the diagnosis of EOPC in our case. However, *IGH* and *FGFR1* gene rearrangements have been reported in up to 37 and 16 % of cases of EOPC. None of the cases showed *CCND1* and *MAF* gene rearrangements [13].

Association of PC with EBV is increasingly recognized [18–21]. The significance of this is not clearly understood. In paper by Saito et al, the authors proposed that EBV positivity and plasmablastic features denote a more aggressive behavior and would render a higher degree of chemosensitivity of the tumor cells [21].

EOPC is considered to be highly radiosensitive, and is commonly treated by irradiation and surgical resection, singly or in combination. The results of this treatment are generally favorable [22, 23]. Our patient was treated with both surgery debulking and radiotherapy. Follow up at 1 year showed that she is free of disease. Of all plasma cell tumors, EOPC has the best prognosis, with a reported 5-year, recurrence-free survival rate of 81 % [24], in particular EOPC involving the head and neck, seems to exhibit

a higher disease-specific survival and overall survival compared to EOPC at other sites [25].

In conclusion, we report an extremely rare case of localized pharyngeal tumefactive amyloidosis caused by extraosseous PC in a 12 year-old girl. The tumor was composed of more than 95 % amyloid with a limited component of well-differentiated neoplastic plasma cells, which were monoclonal (kappa restricted) on light chain ISH. The amyloid deposits were positive for kappa immunoglobulin light chain on immunohistochemistry. The patient was treated with a combination of surgery and radiotherapy. At 1-year follow-up, there has been no evidence of recurrence. Practicing pathologists should have a high level of awareness in diagnosing PC in the presence of amyloid deposits, even in the pediatric population.

Conflict of interest The authors declare that they have no conflict of interest. This work has no specific funding.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- McKenna RW, Kyle RA, Kuehl WM, et al. Plasma cell neoplasms. In: Swerdlow SH, Campo E, Harris NL, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008. p. 200–13.
- Rutherford K, Parsons S, Cordes S. Extramedullary plasmacytoma of the larynx in an adolescent: a case report and review of the literature. *Ear Nose Throat J*. 2009;88:E1–7.
- Naples J, Isseroff TF, Pitman MJ, et al. Laryngeal extramedullary plasmacytoma in an adolescent. *Int J Pediatr Otorhinolaryngol Extra*. 2014;9:33–5.
- Chang YL, Chen PY, Hung SH. Extramedullary plasmacytoma of the nasopharynx: a case report and review of the literature. *Oncol Lett*. 2014;7:458–60.
- Mann G, Trebo MM, Minkov M, et al. Extramedullary plasmacytoma of the adenoids. *Pediatr Blood Cancer*. 2007;48:361–2.
- Vanan I, Redner A, Atlas M, et al. Solitary extramedullary plasmacytoma of the vocal cord in an adolescent. *J Clin Oncol*. 2009;27:244–7.
- Nagasaka T, Lai R, Kuno K. Localized amyloidosis and extramedullary plasmacytoma involving the larynx of a child. *Hum Pathol*. 2001;32:132–4.
- González GI, Diez GL, Rodríguez AN, et al. Extramedullary plasmacytoma of the larynx: a case report. *Acta Otorrinolaringol Esp*. 2011;62:320–2.
- Kruse K, Stein H, Hitzig WH, et al. Lymph node plasmacytoma in a child: clinical and immunological findings with special reference to S-Ig and complement receptor subtypes. *Eur J Pediatr*. 1978;129:239–57.
- Mazziotti MV, Langer JC. Laparoscopic full thickness intestinal biopsies in children. *J Pediatr Gastroenterol Nutr*. 2001;33:54–7.
- Saad R, Raab S, Liu Y, et al. Plasmacytoma of the larynx diagnosed by fine-needle aspiration cytology: a case report. *Diagn Cytopathol*. 2001;24:408–11.
- Lorsbach RB, Hsi ED, Dogan A, et al. Plasma cell myeloma and related neoplasms. *Am J Clin Pathol*. 2011;136:168–82.
- Bink K, Haralambieva E, Kremer M, et al. Primary extramedullary plasmacytoma: similarities with and differences from multiple myeloma revealed by interphase cytogenetics. *Hematologica*. 2008;93:623–6.
- Seegmiller AC, Xu Y, McKenna RW, Karandikar NJ. Immunophenotypic differentiation between neoplastic plasma cells in mature B-cell lymphoma vs plasma cell myeloma. *Am J Clin Pathol*. 2007;127:176–81.
- Ryan RJH, Sloan JM, Collins AB, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with amyloid deposition. A clinicopathologic case series. *Am J Clin Pathol*. 2012;137:51–64.
- Iseri M, Ozturk M, Ulubil SA. Synchronous presentation of extramedullary plasmacytoma in the nasopharynx and the larynx. *Ear Nose Throat J*. 2009;88:E9–12.
- Lewis L, Thomas R, Grace R, et al. Extramedullary plasmacytomas of the larynx and parapharyngeal space: imaging and pathologic features. *Ear Nose Throat J*. 2007;86:567–9.
- Yan B, Tan SY, Yau EX, et al. EBV-positive plasmacytoma of the submandibular gland—Report of a rare case with molecular genetic characterization. *Head and Neck Pathol*. 2011;5:389–94.
- Tomita Y, Ohsawa M, Hashimoto M, et al. Plasmacytoma of the gastrointestinal tract in Korea: higher incidence than in Japan and Epstein-Barr virus association. *Oncology*. 1998;55:27–32.
- Aguilera NS, Kapadia SB, Nalesnik MA, et al. Extramedullary plasmacytoma of the head and neck: use of paraffin sections to assess clonality with in situ hybridization, growth fraction, and the presence of Epstein-Barr virus. *Mod Pathol*. 1995;8:503–8.
- Saito M, Morioka M, Izumiyama K, et al. Epstein-Barr virus-positive ileal extraosseous plasmacytoma containing plasmablastic lymphoma components with CD20-positive lymph node involvement. *Int J Gen Med*. 2012;5:715–8.
- Alexiou C, Kau RJ, Dietzfelbinger H, et al. Extramedullary plasmacytoma: tumor occurrence and therapeutic concepts. *Cancer*. 1999;85:2305–14.
- Susnerwala SS, Shanks JH, Banerjee SS, et al. Extramedullary plasmacytoma of the head and neck region: clinicopathological correlation in 25 cases. *Br J Cancer*. 1997;75:921–7.
- Bachar G, Goldstein D, Brown D, et al. Solitary extramedullary plasmacytoma of the head and neck—Long-term outcome analysis of 68 cases. *Head Neck*. 2008;30:1012–9.
- Gerry D, Lentsch EJ. Epidemiologic evidence of superior outcomes for extramedullary plasmacytoma of the head and neck. *Otolaryngol Head Neck Surg*. 2013;148:974–81.