Non-immune hydrops fetalis associated with two umbilical cord hemangiomas and vascular malformation of the transverse mesocolon. Case report

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SUMMARY
Umbilical cord hemangioma is a rare tumor that can be associated with significant fetal and perinatal complications. Although usually described as a single anomaly, sometimes these tumors are reported in association with other vascular lesions. We report an unusual case of simultaneous occurrence of two umbilical cord hemangiomas and vascular malformation of the transverse mesocolon in a stillborn fetus with hydrops. To our knowledge, this is the first report of two simultaneously occurring umbilical cord hemangiomas. Moreover, presence of associated vascular malformation of transverse mesocolon could support the hypothesis of underlying predisposition to the development of vascular tumors.

Keywords: hydrops fetalis – hemangioma – umbilical cord – stillbirth – vascular malformation – transverse mesocolon

Neimunitní hydrops plodu asociovaný se dvěma hemangiomy pupečníku a vaskulární malformací mesocolon transversum - popis případu

SOUHRN
Hemangiom pupečníku je vzácný benigní nádor, který může být asociován s významnými fetálními a perinatálními komplikacemi. Ačkoli jsou hemangiomy pupečníku často popisovány jako izolované nálezy, v některých případech se mohou vyskytovat společně s jinými cévními lézemi. V našem kazuistickém sdělení popisujeme neobvyklý případ mrtvě porozeného plodu s povšechným hydropsem, u nějž byly pitvou prokázány dva hemangiomy pupečníku a cévní malformace mesocolon transversum. Jedná se o raritní, a podle nám dostupných informací, i první případ současného výskytu dvou hemangiomů pupečníku. Přítomnost přidružené cévní malformace mesocolon transversum by navíc mohla podporovat hypotézu, že hemangiomy pupečníku jsou součástí stavů predisponujících ke vzniku cévních nádorů a malformací.

Klíčová slova: hydrops plodu – hydrops fetalis – hemangiom – pupečník – mrtvorozenost – vaskulární malformace – mesocolon transversum

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The presence of hydrops fetalis generally portends a poor prognosis, with substantial risks of intrauterine fetal demise, preterm labor, and neonatal morbidity and mortality. Once this condition is identified, it is important to systematically perform the differential diagnosis. The majority of cases are non-immune in nature, and wide variety of causes are known to lead to non-immune hydrops fetalis (1-4). Umbilical cord lesions associated with vascular constriction and/or obstruction are considered to be the rare causes of hydrops fetalis (2,5,6).

Umbilical cord hemangiomas are benign vascular tumors usually presenting as a fusiform swelling within the cord with presence of an angiomatous nodule on cut surface (7-9). Although morphologically umbilical cord hemangiomas are very similar to the more common placental hemangiomas (chorangiomas), the frequency of the former lesion is much lower than that of placental hemangiomas (7-15). This is the first case we have seen in our practice, although hundreds of placentas are examined yearly in our institute.

Histologically, the tumor is composed of anastomosing vascular structures, lined by endothelium, and surrounded usually by a myxoid or mucoid stroma (7,8,12,13,16). The etiology of umbilical cord hemangiomas remains unclear. Previous studies reported no apparent association between fetal sex, maternal age, race, or gravidity, and development of cord hemangiomas (7,10,13). These tumors typically occur as an isolated anomaly, although they have been also described in association with other malformations, including skin and systemic hemangiomas (9,11,15,17).

Here we report an unusual case of two umbilical cord hemangiomas and associated vascular malformation of transverse mesocolon in a stillborn male fetus with hydrops.

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CASE REPORT

A 34-year-old Asian woman, gravida 4, para 1, with a medical history of two missed abortions and one spontaneous full

term delivery of a child diagnosed with DiGeorge syndrome, had a routine ultrasound scan at 22 weeks that showed polyhydramnios and hydrops fetalis. Moreover, ultrasound examination demonstrated a hyperechogenic mass within the umbilical cord measuring approximately 3 x 2 cm (Fig. 1). The mass was located near the fetal insertion of umbilical cord. No other abnormalities were detected. The fetal abdominal wall was intact. Hematogenous infections associated with non-immune hydrops fetalis as well as Rh isoimmunization were excluded. Amniocentesis was performed. Amniotic fluid cells showed normal 46, XY male karyotype. Levels of maternal serum alpha-fetoprotein were normal. At 28 weeks the woman felt decrease of fetal movements and saw her gynecologist. Ultrasound examination showed no fetal heartbeat. The woman was referred to the hospital and one day later she delivered a male fetus with no signs of life after medical induction with prostaglandins at 28+6 weeks of gestation.

The macerated fetus was 40 cm long and weighted 2560 g. The autopsy showed an excessive accumulation of serous fluid in the fetal tissues and body cavities. Bilateral pulmonary hypoplasia was present. In the transverse mesocolon there was found an edematous vascularized mass measuring approximately 4 cm in the largest dimension. Umbilical cord was 68 cm long. Approximately 1 cm from fetal insertion, there was an ovoid solid mass with smooth surface measuring 3 x 2 x 1.5 cm (Fig. 2). The cut surface of the lesion revealed a numerous blood-filled vascular channels (Fig. 3A). The Wharton's jelly adjacent to the lesion was edematous. In the placental insertion site of the umbilical cord, there was surprisingly found another similar lesion

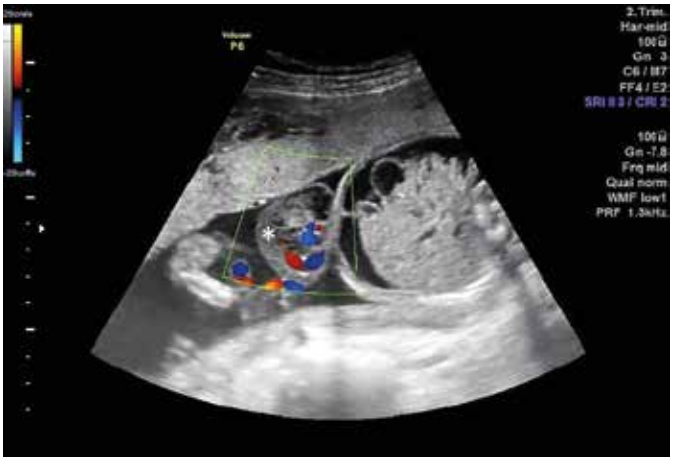

Fig. 1. Ultrasound scan showing hyperechogenic mass (white asterisk) within umbilical cord.

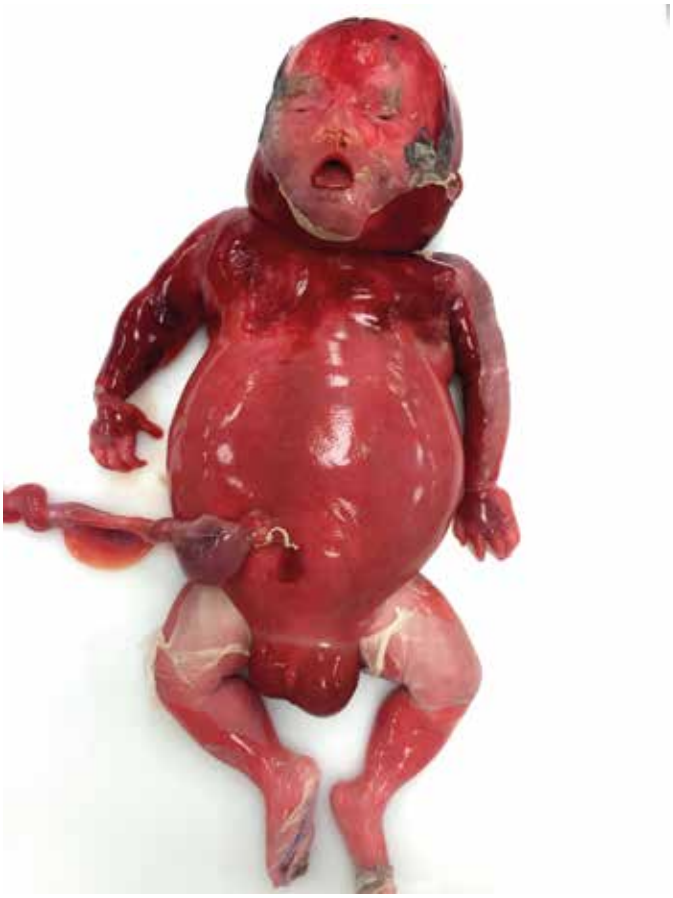

Fig. 2. Macerated fetus with an ovoid mass (hemangioma) within edematous umbilical cord.

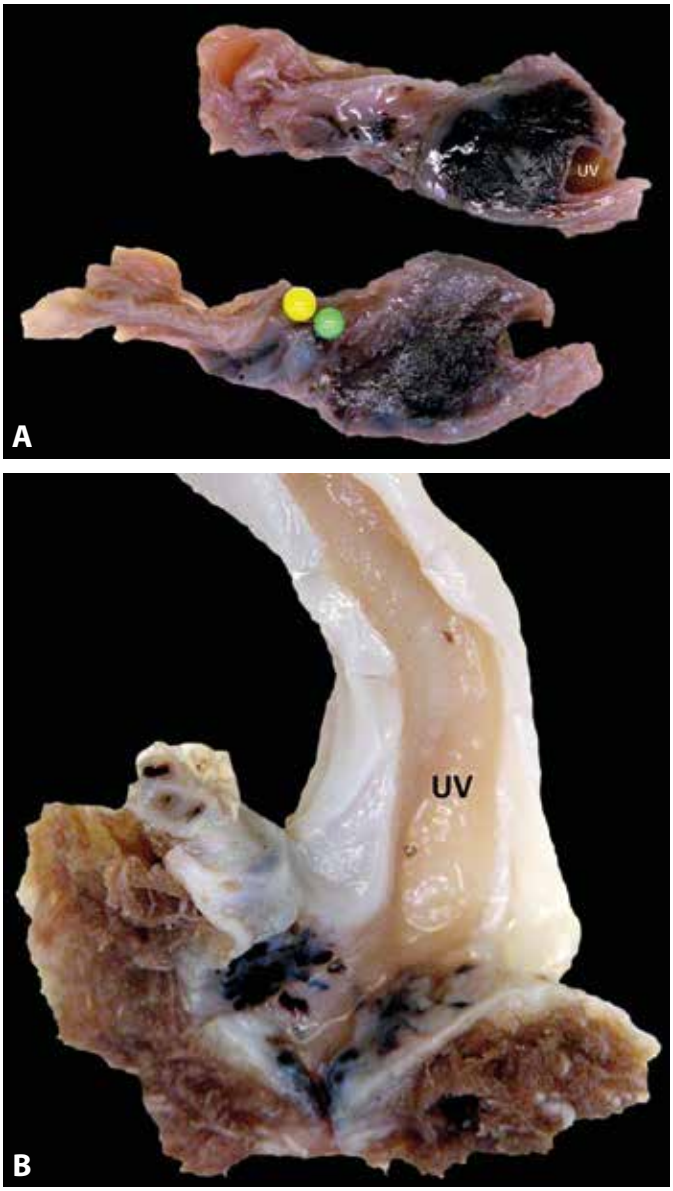

Fig. 3. Macroscopic appearance of umbilical cord hemangiomas. (**A**) Larger hemangioma near fetal cord insertion. Cut surface revealed vascularized mass in close contact with umbilical vein (UV). Green and yellow pins show umbilical arteries. (**B**) Smaller hemangioma in the placental insertion site encircling umbilical vein (UV).

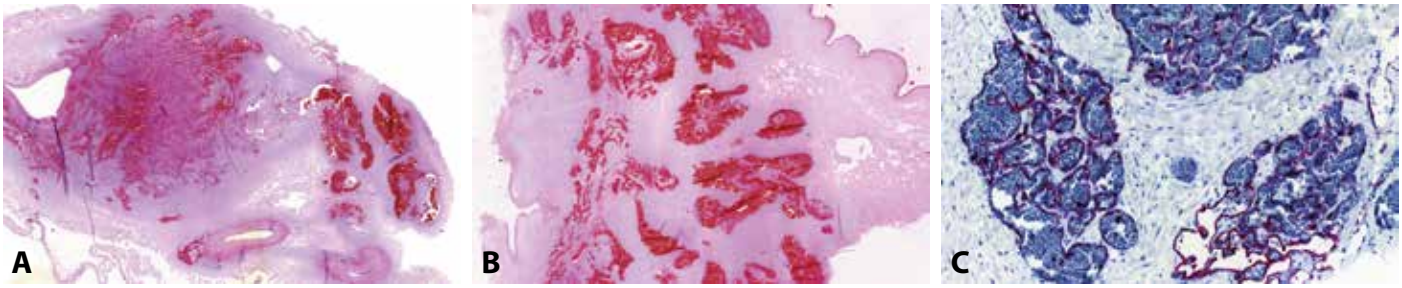

Fig. 4. Microscopic appearance of umbilical cord hemangiomas. (**A**) Larger hemangioma composed of multiple arborizing blood vessels surrounding umbilical vein (HE, 40x). (**B**) Smaller hemangioma consisting of multiple small thin-walled vascular channels (HE, 40x). (**C**) Vascular structures are lined by endothelium positive for CD31 (CD31, 400x).

measuring 1.1 x 1 x 1 cm, and consisting of multiple small vascular channels (Fig. 3B). Placenta was pale and enlarged, it weighted 450 g and measured 19 x 17 x 3 cm.

Histologically, both umbilical cord masses were composed of numerous small branching vessels proliferating in the background of myxoid stroma of Wharton's jelly. Vascular channels were lined by flattened endothelium positive for CD31 and CD34 (Fig. 4A, 4B and 4C). The lesions fulfilled the pathological criteria of an umbilical cord hemangioma. Both hemangiomas were in the close contact with the wall of umbilical vein. Neither calcification, thrombosis nor osseous metaplasia were present. Examination of placenta showed chorionic villi with stromal edema and increased numbers of Hofbauer cells and changes consistent with intrauterine fetal demise, including intravascular karyorrhexis. Vascular malformation of the transverse mesocolon was composed of multiple dilated vascular structures of variable size and thickness of the wall (Fig. 5A and 5B). The lesion was not encapsulated but relatively well demarcated from surroundings.

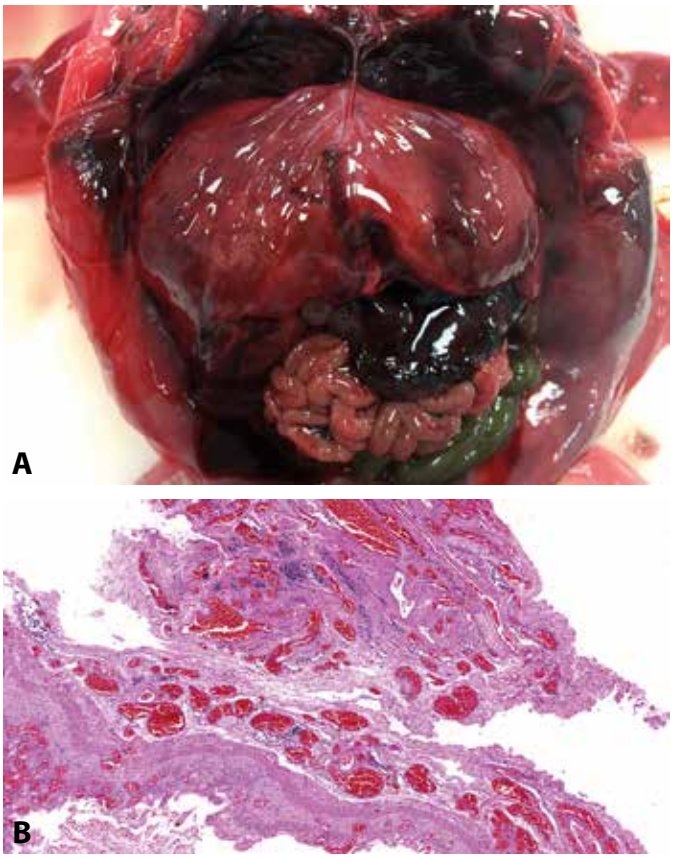

Fig. 5. Vascular lesion of transverse mesocolon. (**A**) Macroscopic appearance. (**B**) Proliferation of dilated vascular structures of various size and wall thickness (HE, 100x).

DISCUSSION

Hydrops fetalis is estimated to occur in 1 per 3000 pregnancies and is traditionally defined as an abnormal accumulation of fluid in at least two fetal compartments, inluding ascites, pleural effusion, pericardial effusion, and skin edema (2,5,18). The majority of cases are non-immune in nature and wide variety of congenital infections, cardiovascular diseases, tumors, genetic causes, maternal diseases or placental and umbilical cord lesions are known to lead to non-immune hydrops fetalis (1-4). The main factors involved in the pathogenesis of fetal hydrops are severe fetal anemia, hypoproteinemia, fetal heart failure and interference with fetoplacental circulation impedance to venous return from placenta (5,19). Placental and umbilical cord lesions that have been associated with non-immune fetal hydrops include chorangiomas, umbilical vein thrombosis, torsion or true knots (1,5,6).

Large placental chorangiomas, measuring more than 5 cm, can act as a high volume arteriovenous shunts and lead to hydrops due to high cardiac output. The increased demand for cardiac output leads to cardiac failure, and corresponding edema. It is assumed that other vascular tumors and malformations can similarly cause non-immune hydrops fetalis (1,6). Umbilical cord lesions associated with umbilical vein constriction and/or obstruction lead to increase in hydrostatic pressure in umbilical vein proximal to obstruction. Initially, the umbilical venous partial obstruction could lead to increase in intravillous capillary pressure resulting in villous edema and subsequent fetal hypoxemia. Later, fetal cardiac function may be impaired because of increase in placental villous pressure. Collectively, it may give rise to fetal hydrops (19,20).

Umbilical cord tumors are rare findings. Only two true tumors of the cord are described: hemangioma and, more rarely, teratoma (7,8,10,13,21). Hemangioma of the umbilical cord is a benign vascular lesion of various size (7-14) usually located near the placental insertion of the cord (7,10,13). Histologically, the tumor is composed of multiple branching vessels surrounded usually by a loose myxoid connective tissue (7,8,12,13,16). Sometimes thrombi, calcifications or osseous metaplasia can be found within the tumor (7,8,10,12). The myxoid appearance has lead some authors to call this lesion angiomyxoma (7,11,22). Edema, myxoid and cystic changes of the Wharton's jelly adjacent to the tumor are nearly constant findings (7-9,12,13,16,17,20). These changes are due to high permeability of angiomatous vessels placed in a gelatinous tissue (7,13). The tumor presumably arises

from one or more of the major umbilical vessels or vitelline capillaries. Some authors hypothesize that umbilical cord hemangioma is a hamartoma rather than a true neoplasia and that it arises as a malformation of the primitive angiogenic mesenchyma of the developing cord (7,8,13,14,23). The etiology of the lesion remains unclear. The most frequent presentation of the tumor is that of isolated fetal anomaly, although it has been repeatedly described in asssociation with skin and visceral hemangiomas (9,11,15,17,24,25). A causal relationship has not been definitely established, but some authors suggest that there could be an underlying predisposition to vascular neoplasms (10,11). Moreover, umbilical cord hemangioma has also been reported in association with Klippel-Trenaunay-Weber syndrome, a condition characterized by a triad of findings: cutaneous hemangiomas, soft tissue and bone hypertrophy, and vascular malformations (26). On the other hand, the gastrointestinal and heart malformations (24), hypospadias (27), anencephaly (28) and limb deformities (29) reported in the literature are probably just random coincidences. Polyhydramnios and increased alpha-fetoprotein have been reported in some cases (10,12,15,29,30).

Although umbilical cord abnormalities can be detected through antenatal ultrasound scans, the definitive diagnosis commonly can not be made because of nonspecific findings. When the umbilical cord abnormalities are suspected, the differential diagnosis should include hematomas, varices, aneurysms, thrombosis, cystic lesions such as omphalomesenteric duct cyst or allantoic cyst, abdominal wall defects and last but not least tumors (10,31).

The possible clinical significance of the umbilical cord hemangioma remains obscure. Most authors report a potential risk of fetal and perinatal morbidity and mortality, especially due to premature delivery, heart failure, severe fetal hemorrhage, non-immune hydrops fetalis and intrauterine death (7,8,13,16,32). It is suggested that mechanical compression of umbilical vessels by a tumor or cord torsion are the most plausible reasons for impairment of umbilical circulation, which is considered as the predisposing factor for poor fetal outcome. In addition, there are several other theories relating to how cord hemangioma affects the umbilical circulation, including acting as a arteriovenous shunt. Progressive edema and cystic degeneration of Wharton's jelly, very frequent findings associated with umbilical cord hemangioma, could also contribute to vessel compression (12,20,23,30,33).

In our case, the compression of umbilical vessels, specifically vein, by two tumors at both insertion sites of the cord, seems to be the most probable cause of circulatory compromise which resulted first in hydrops fetalis and subsequently in fetal intrauterine death. To the best of our knowledge, this is the first report describing two simultaneously occurring hemangiomas of the umbilical cord. A PubMed search of the literature published since 1951 revealed no similar case. Moreover, the presence of an associated vascular malformation of transverse mesocolon could support the hypothesis of underlying predisposition to vascular neoplasms.

CONCLUSION

Despite its rarity, one should be familiar with existence and clinical significance of this tumor. Once identified prenatally, the mother should be counseled for possible fetal complications. If detected in the neonatal period, infants should be carefully examined with the knowledge that associated vascular lesions may be present.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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MONITOR
aneb **nemělo by vám uniknout, že ...**

HEMATOPATOLOGIE

... mezi MGUS a myelomem se objevuje MGRS

Nádory z plazmocytů tvoří kontinuum od relativně benigních prekurzorových lézí až po jasně maligní nádory. Na jednom pólu stojí monoklonální gamapatie nejistého významu (monoclonal gammopathy of undetermined significance, MGUS). Ta je definována průkazem paraproteinu v séru v koncentraci nižší než 30 g/l, méně než 10 % klonálních plazmocytů ve dřeni a nepřítomností orgánového postižení definovaného zkratkou CRAB (hyperkalcémie pro C, renální insuficience pro R, anémie pro A a kostní léze pro B). Neprokazuje se ani AL amyloidóza.

Na opačném pólu spektra je plazmocelulární myelom, dříve známý též jako mnohotný myelom a mezi námi pamětníky i Kahlerova nemoc. Diagnostická kritéria jsou postavena na průkazu více než 10 % klonálních plazmocytů ve dřeni, resp. na histologickém potvrzení plazmocytomu v kombinaci s postižením orgánů, tedy alespoň jednoho projevu ze spektra CRAB.

Něco mezi je plazmocytom bez orgánového postižení, který se označuje asymptomatický nebo více poeticky doutnající plazmocytom.

Odlišení těchto kategorií je klinicky významné, neboť terapie je indikována pouze u symptomatických pacientů s orgánovým postižením, bez něj se doporučuje pouze sledování.

Analogická je situace u dalších onemocnění, které vedou k produkci patologických monoklonálních imunoglobulinů. Napadne vás jistě lymfoplazmocytický lymfom (LPL) na agresivnější straně spektra a IgM-pozitivní MGUS na straně druhé, oba spojené téměř pravidelnou mutací genu *MYD88*. Terapie se obvykle indikuje při více než 10% postižení dřeně a výskytu alespoň jednoho projevu (anémie, trombocytopenie, kryoglobulinémie či hyperviskozní syndrom).

V Monitoru (02/2018) jsme již zmiňovali monoklonální B lymfocytózu (MBL) jako možný prekurzor B-CLL, která také může být spojena s paraproteinem.

Až potud krásná úhledná a nalajnovaná teorie. A pak přijde život! A život přináší pacienty s myelomovou ledvinou, tedy renálním postižením z definice asociovaným s myelomem, ale ten se nedaří prokázat. Je chybou nazvat renální postižení „idiopatické", protože to za prvé není pravda (monoklonální gamapatie je evidentně přítomna) a za druhé to může být pochopeno jako benigní onemocnění. Navíc v běžném terapeutickém rozhodování u LPL či CLL izolované renální postižení nepatří mezi kritéria k zahájení léčby. V teorii se objevuje díra! Závažná díra.

Jak tuto díru vyplnit popisuje mezinárodní skupina autorů v přehledovém článku v NEJM. Řešením je koncept MGRS, tedy monoklonální gamapatie s renálním významem. Jedná se o postižení ledvin spojené s premaligní klonální gamapatií, která by sama o sobě nevyžadovala léčbu, ale s ohledem na renální insuficienci je chemoterapie zaměřená na patologický klon zcela oprávněná. MGRS se tak stává jednou z nejdůležitějších součástí tzv. monoklonální gamapatie s klinickým významem (monoclonal gammopathy of clinical significance, MGCS) spojené s malými, ale nebezpečnými klony B buněk souhrnně popsané již před několika lety v časopisu Blood. Zájemce o vyčerpávající (a to doslova!) popis patogeneze postižení ledvin a ostatních tkání monoklonálními imunoglobuliny odkazuji na tyto zdroje.

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- V. Campr -