[Matusz et. al., Vol.6 (Iss.9): September 2018] ISSN- 2350-0530(O), ISSN- 2394-3629(P)
(Received: September 01, 2018 - Accepted: September 29, 2018) DOI: 10.5281/zenodo.1464999

INTERNATIONAL JOURNAL OF RESEARCH – GRANTHAALAYAH
A knowledge Repository

Science

THE UNEXPECTED MEDIASTINAL EXTENSION IN A CASE OF LUNG CANCER: THE ROLE OF IMAGING AND MULTIPLE SIDE-EFFECTS WITH CLINICAL RELEVANCE FOLLOWING TOPIRAMATE THERAPY

Daniela Cipu [1], Dan Simion Cipu [2], Agneta Maria Pusztai [3], Anca Alexandra Matusz [4]
[1] Radiology and Imaging Department, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Timis County, Romania
[2] Timis County Center of the Ministry of the Internal Affairs, Timisoara, Romania
[3] Anatomy and Embriology Department, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Timis County, Romania
[4] M.D., General Practitioner Children@Adults, Timisoara, Timis County, Romania

Abstract

Bronchopulmonary neoplasm is the first cause of cancer mortality in the world and a major public health problem, affecting 17% of men and 12% of women; in this context it is very important and necessary to establish the correct diagnosis in the early stages of the disease in order to initiate the required surgical therapy [1].

Keywords: Unexpected; Mediastinal; Relevance; Clinical.

Cite This Article: Daniela Cipu, Dan Simion Cipu, Agneta Maria Pusztai, and Anca Alexandra Matusz. (2018). "THE UNEXPECTED MEDIASTINAL EXTENSION IN A CASE OF LUNG CANCER: THE ROLE OF IMAGING AND MULTIPLE SIDE-EFFECTS WITH CLINICAL RELEVANCE FOLLOWING TOPIRAMATE THERAPY." *International Journal of Research - Granthaalayah*, 6(9), 478-486. https://doi.org/10.5281/zenodo.1464999.

1. Introduction

In our previous studies performed on 134 patients, we revealed that the comparative evaluation of the effectiveness of imaging methods in the diagnosis of malignant pulmonary pathology and mediastinal lymphadenopathy pointed out the superiority of the CT scan over the conventional radiographic exam at the level of the superclavicular, anterior mediastinal and the aortic-pulmonary window [2].

The radiographic examination options to monitor bronchial-pulmonary neoplasia are still useful and commonly applied in the clinical practice, detecting both tumor behavior and side-effects of radiotherapy [3].

ISSN- 2350-0530(O), ISSN- 2394-3629(P)
(Received: September 01, 2018 - Accepted: September 29, 2018) DOI: 10.5281/zenodo.1464999

Topiramate (TPM) is an antiepileptic drug, synthesized in an effort to find a blocking agent for gluconeogenesis [4]. It was first approved for prescription use in 1996 and proved its effectiveness in the last decade against migraine headaches and became a potent therapeutic remedy for chronic pain in patients with cancer [5].

From a chemical point of view, it is a substituted sulphamate monosaccharide of molecular formula C12H21NO8S (339.37 g/mol). Topiramate (**Figure 1**) (has 2,3,4,5-bis-O- (1-methylethyldiene) - β-D-fructopyranose sulfamate as active substance represented by the formula:

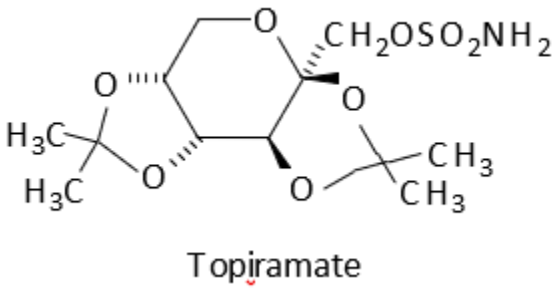

Figure 1: Chemical structure of topiramate.

TPM is presented as 15 mg and 25 mg hard capsules as well as immediate release tablets of 25 mg, 50 mg, 100 mg and 200 mg.

Although TPM is usually safe and well-tolerated, in most cases the optimum dose does not exceed 400 mg/day. Thus, the occurrence of adverse events requires discontinuation of treatment and limits its use in about 25% of patients [6], [7].

2. Case Report

Illustrative for the capricious evolution of bronchopulmonary carcinoma is the case of the 49-year-old patient (P.E.), who was hospitalized for a confirmed pneumonic symptomatology and condensation in the lower left lobe.

During hospitalization, under antibiotic and anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAID's), the pneumonic process tends to diminish, but is further accompanied by the appearance of multiple voluminous centro-hilar and left hilar opacities, interpreted as a tumor, respectively a lymphadenopathy which was confirmed as such by a CT examination performed in the CT Laboratory belonging to the Military Hospital in Timisoara (Figure 2):

ISSN- 2350-0530(O), ISSN- 2394-3629(P)
(Received: September 01, 2018 - Accepted: September 29, 2018) DOI: 10.5281/zenodo.1464999

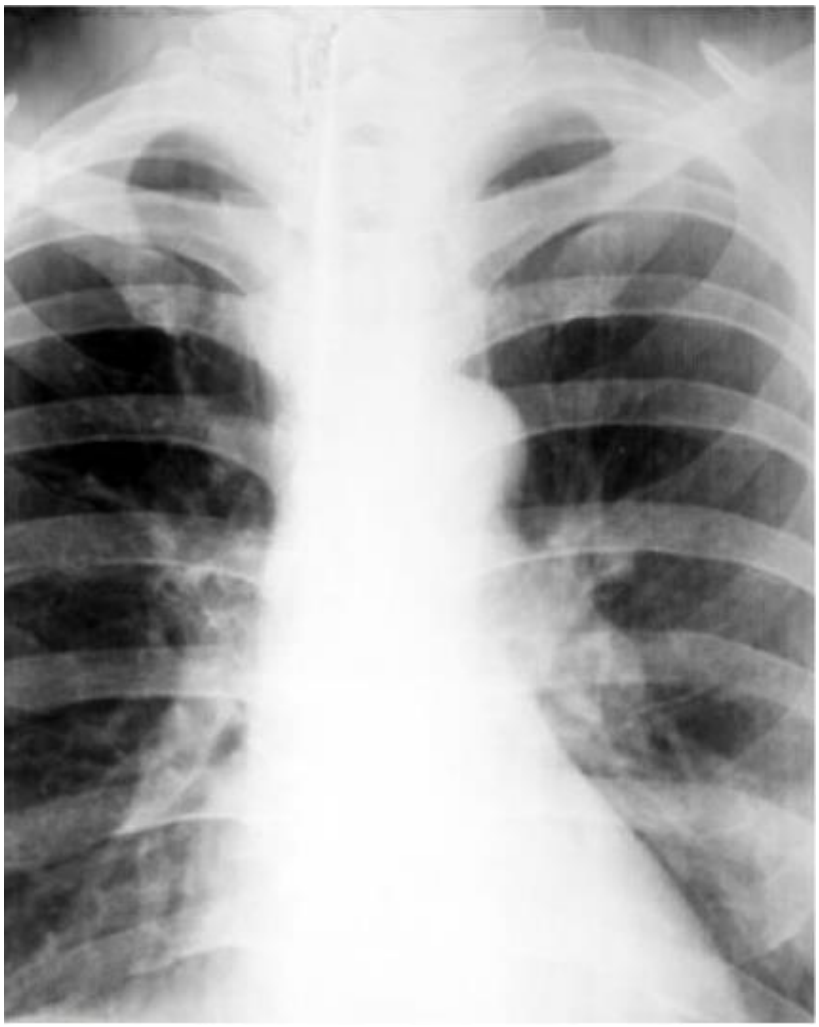

Figure 2: Condensation of the left inferior lobe with lymphadenopathy and left hilar tumor formation detected on the chest X-ray and confirmed by the CT examination.

Radical surgery was decided and was performed in the evolution after pneumonectomy was aggravated by the occurrence of vertebral metastases accompanied by a severe hyperalgesic syndrome and long lasting recurrent neuropatic pain.

A verbal pain linear analogue assessment scale was used to assess neuropathic pain, as described in the literature [8]. Pain medication history was also reviewed in addition to detecting co-morbidities. The following variables were extracted from the medical record: pain characteristics, location, date of initiation of therapy for each drug, maximal tolerated dose, other concurrent medications, number of months of pain before initiation of topiramate therapy and the development of adverse effects.

Topiramate was administered as a third-line pain relief treatment in this patient for a period of nine month, as monotherapy, in a dosis of 200 mg/day. The doses of topiramate administered were within therapeutic limits, being progressively increased. From the heredocolateral and personal antecedents no other pathological conditions have been noted (no stone disease or any ophtalmic

ISSN- 2350-0530(O), ISSN- 2394-3629(P)
(Received: September 01, 2018 - Accepted: September 29, 2018) DOI: 10.5281/zenodo.1464999

problem). At the end of the studied period, the patient experienced multiple and severe adverse events, which required to discontinue topiramate therapy.

In this context, evolving under the treatment, a severe alkalinisation of the urine that did not yield to the usual hygienic-dietary measures (diuretic cure, citrate administration, hypnosis diet) occurred. Full urine test and urinary pH monitoring were performed weekly. The patient presented recurrent urinary infections with *Bacillus Proteus*. After 9 months of treatment, the patient eliminated a kidney stone consisting of magnesium phosphate and ammonium hexahydrate, as determined by Fourier Transform Infrared Spectroscopy (FTIR) (Figure 3):

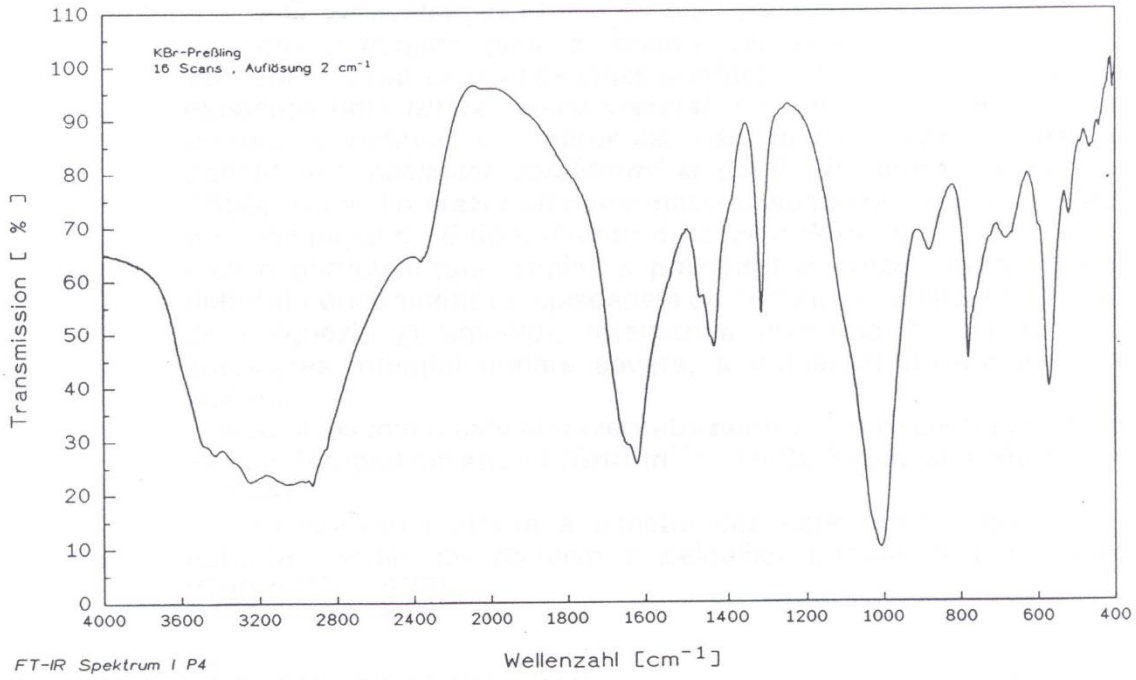

Figure 3: FIRT absorption spectrum of the renal stone composed of magnesium phosphate and ammonium hexahydrate (struvite), eliminated after nine month treatment with topiramate.

The renal concretion had the following morphological and mineralogical characteristics:

- location: right ureter;
- exterior appearance: coral look, white-yellow color, smooth surface;
- section view: homogeneous;
- consistency: reduced, highly friable;
- dimensions: 0.5 / 0.4 cm;
- weight: 0.195 g;
- number: unique ureteral calculus.

The FIRT absorption spectrum of a fragment taken from the ureteral calculus revealed 18 absorption bands; among these, 10 of are characteristic for magnesium and ammonium phosphate hexahydrate, with the mineralogical name of *struvite*: 467, 572, 781, 1008, 1435, 1623, 2366, 2924, 3057 and 3247 cm^{-1} (Figure 3 and Table 1):

ISSN- 2350-0530(O), ISSN- 2394-3629(P)
DOI: 10.5281/zenodo.1464999

Table 1: Automatic listing of absorption bands of the renal calculus removed from patient P.B, 49 years

P.4. SP 3601 4000.00 400.00 9.93 100. 87 192.78 %T 16 SD									
REF 4000 64.87 2000 95.81									
3421.00	**27.50**	**3247.00**	**22.42**	**3057.00**	**21.97**	**2924.00**	**21.76**	**2360.00**	**63.51**
1623.00	**25.50**	**1435.00**	**47.26**	**1316.00**	**53.49**	**1008.00**	**9.93**	**880.00**	**65.00**
781.00	**44.86**	**684.00**	**67.09**	**572.00**	**39.62**	**521.00**	**71.50**	**467.00**	**33.94**
442.00	**87.88**	**413.00**	**99.46**	**407.00**	**95.03**				
END 18 peak(s) found									

Six month after the onset of treatment, the patient also experienced other associated side effects, namely:

- significant weight loss (3 kg weight deficit);
- severe myopia with acute onset;
- leucopenia and recurrent epistaxis.

It was found that discontinuation of topiramate therapy resulted in spectacular disappearance of renal manifestations as well as other adverse reactions, with the normalization of all previously modified parameters.

3. Discussion

From an imagistic point of view, the presented case is special because the normal hilar lymph nodes located in the bronchial gap between the bronchi and the pulmonary vessels are often very difficult to differentiate from it, because they cause some margins of the right or concave incision to the pulmonary parenchyma [9].

This diagnostic exploration was based on the identification of the specific relation of the hilar lymph nodes with the gap in their neoplastic infiltration, defining it convexly to the pulmonary parenchyma due to the inflammatory response caused by carcinoma lymphangitis [10].

Topiramate is effective as monotherapy in adults and children. Because a therapeutic effect emerges during titration, clinicians should adjust dosages in step-wise fashion with intermediate stopping points, e.g., 100 mg/day, to evaluate patient response and achieve the optimal maintenance dosage [11].

The mechanism by which topiramate exerts therapeutic antiepileptic and analgesic action is incompletely elucidated. Electrophysiology and biochemistry studies on neural cultures have identified three properties that can contribute to the antiepileptic efficacy of topiramate:

- blocking voltage-dependent sodium channels [12];
- favoring GABA-ergic type inhibitory transmission [13];
- inhibition of carbonic anhydrase enzymes, especially isoenzymes II and IV [14].

ISSN- 2350-0530(O), ISSN- 2394-3629(P)
(Received: September 01, 2018 - Accepted: September 29, 2018) DOI: 10.5281/zenodo.1464999

The pharmacokinetic profile of topiramate is different from that of other antiepileptic drugs, differentiating between long plasma half-life, linear pharmacokinetics, predominantly renal clearance, low plasma protein binding, and lack of clinically relevant metabolites [15, 16].
Oral bioavailability is 80%, not related to food intake. Following oral administration, topiramate is rapidly and completely absorbed; Peak plasma concentration (Cmax) of 1.5 μg / mL is reached 2 hours after a 100 mg dose (Tmax).

After administration, it is bound to plasma proteins in a reduced proportion of only 13-17%. Topiramate increase in plasma concentrations is accompanied by a decrease in the plasma protein fraction [17], [18]. The volume of distribution is 0.55 l/kg; it varies inversely with the dose of administered topiramate. Six metabolites formed following the hydroxylation, hydrolysis and glucuronidation processes have been identified. Metabolism of topiramate is performed up to 50% with coadministration of anticonvulsant-inducing enzyme systems.

An important aspect relates to the hepatic oxidation of topiramate. Unlike other epileptics, this anticonvulsant drug has a complex mechanism of action; thus, it possesses the enzymatic induction capacity by the CYP3A4 cytochrome and the enzymatic inhibitory capacity by the cytochrome CYP2C19. [19].

The primary route of elimination of topiramate is the renal route. Thus, it is known that, in the absence of hepatic enzyme induction, 50% -80% of a given dose is excreted in the urine as such, unchanged [20]. 30% of the administered dose is eliminated by the liver. There are clinical trials demonstrating tubular reabsorption of topiramate [21].

The clearance of topiramate is age-dependent. Thus, the median half-life is 19-23 hours in adults and 15.4 hours in children, and serum concentrations of topiramate are usually 33% lower in children than in adults [5].

Topiramate is not a potent inducer of enzyme systems; therefore, does not require monitoring of plasma concentrations. In the many clinical trials in which the therapeutic efficacy was tested, no correlation between plasma concentration and therapeutic efficacy or severity of adverse reactions was found [22].

Numerous clinical trials have highlighted the tendency of topiramate to favor iatrogenic lithiasis and metabolic acidosis [23], [24]. In addition to anticonvulsant action, it also acts as inhibitor of certain carbonic anhydrase enzymes (CA-II and CA-IV). Wilner et al [25] noted that 5% of patients treated with topiramate eliminated renal calculi. Kuo et al. [26] investigated the nature of the calculi produced by topiramate and found that most of them were made up of phosphates. This fact supports the hypothesis that topiramate would produce the consequent metabolic acidosis, which produces hypocytraturia and an intense alkalinization process of the urine. Some patients associate also oliguria and a prolonged febrile syndrome.

It is important to reveal that the ureteral stone developed under conditions of relapsing urine recurrence with *Bacillus Proteus*. By correlating FTIR spectroscopy with the clinical context of disease evolution, we note the importance of alkaline urinary pH as a factor favoring the multiplication of ureolytic germs, as noted in our previous researches [27].

ISSN- 2350-0530(O), ISSN- 2394-3629(P)
(Received: September 01, 2018 - Accepted: September 29, 2018) DOI: 10.5281/zenodo.1464999

Patient P.B. also experienced severe leucopenia (3000-3500/mmc) and myopia, evident after the first month of treatment. It is noted that leucopenia is produced due to the extremely rapid adjustment of the therapy; leucopenia had clinical relevance through numerous respiratory infections which occurred during the studied period.

A fear-induced complication of topiramate is acute glaucoma, with rapid onset and irreversible evolution. Clinical trials in the literature have reported this complication. Severe rapid myopia after one month of treatment has a severe prognosis and requires reconsideration of treatment [28]. The neuropsychiatric manifestations noted in this case were represented by drowsiness and fatigue. According to the literature, they correlate with the administered topiramate dose [29].

The untreated metabolic acidosis with chronic evolution determines nephrolithiasis and osteomalacia affecting the weight curve as in the case presented above.

Clinical follow-up of patients with their regular biological monitoring prevents the occurrence of topiramate-induced adverse reactions of clinical relevance.
The most important laboratory tests are:

- complete blood count;
- complete urine tests and especially urinary pH monitoring;
- hepatic testes;
- glycemia, natremia and alkaline phosphatase.

4. Conclusion

In conclusion, the presented case is suggestive for the topiramate safety, and the adverse events are in relationship with the administered doses. The side effects of clinical relevance are: lithogenous action, weight loss, acute myopia, and leukopenia.

As a new analgesic drug with increasing applicability in oncology, it is recommended that the practitioner carefully monitors these reactions, due to the fact that some of them are of particular gravity and are difficult to recognize in clinical practice.

References

[1] Tammemägi M.C. (2015) Application of risk prediction models to lung cancer screening: a review. J Thorac Imaging, Mar;30(2), 88-100. https://doi.org/10.1097/RTI.0000000000000142.
[2] Cipu C. Daniela (2015) Value of radio-imagistic explorations in the assessment of mediastinal lung cancer extension, with the emphasis on the computed tomography examination, in the lesion balance and the quantification of staging. PhD Thesis, elaborated at "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania.
[3] Selva A., Bolibar I., Torrego A., Pallarès M.C. (2014) Impact of a program for rapid diagnosis and treatment of lung cancer on hospital care delay and tumor stage. Tumori, Nov-Dec; 100(6), e 243-9. https://doi.org/10.1700/1778.19286.
[4] Biton V., Montouris G.D., Ritter F. (1999) A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group, Neurology, 52, 1330-1337.

[5] Faught E. (2007) Topiramate in the treatment of partial and generalized epilepsy. Neuropsychiatr Dis Treat, Dec; 3(6), 811-821.
[6] Arroyo S, Dodson W.E., Privitera M.D. (2005) Randomized dose-controlled study of topiramate as first-line therapy in epilepsy. Acta Neurol Scand, 112, 214-222.
[7] Meador K.J., Loring D.W., Vahle V.J. (2005) Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. Neurology. 64, 2108-2014.
[8] Bendaly E.A., Jordan C.A., Staehler S.S., Rushing D.A. (2007) Topiramate in the treatment of neuropathic pain in patients with cancer. Support Cancer Ther, Sep 1;4(4), 241-246. https://doi.org/10.3816/SCT.2007.n.021.
[9] Gruden J.F., Webb W.R., Naidich D.P., McGuiness G. (1999) Multinodular disease: anatomic localization at thin-section CT-multireader evaluation of a simple algorithm. Radiology, Mar 210(3), 711-720. https://doi.org/10.1148/radiology.210.3r99m21711.
[10] Sheth S., Hamper U., Stanley D.B., Wheeler J.H., Smith P.A.(1999) US guidance for thoracic biopsy: a valuable alternative to CT. Radiology, Mar 210(3), 721-726.
[11] Wiffen P.J., Derry S., Lunn M.P., Moore R.A. (2013) Topiramate for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. Aug 30;(8), CD008314. doi: 10.1002/14651858.CD008314.pub3.
[12] Shank R.P., Gardocki J.F., Streeter A.J. (2000) An overview of the pre-clinical aspects of topiramate: pharmacokinetics, and mechanism of action. Epilepsia, 41Suppl 1, 53-59.
[13] Rosenfeld W.E., Doose D.R., Walker S.A. (1999) A study of topiramate pharmacokinetics and tolerability in children with epilepsy. Pediatr Neurol, 20, 339-344.
[14] Gisclon L.G., Riffits J.M., Sica D.A. (1993) The pharmacokinetics (PK) of topiramate (T) in subjects with renal impairment (RI) as compared to matched subjects with normal renal function (NRF). Pharmaceutical Research, 10, S397.
[15] Reife R.A., Pledger G.W. (1997) Topiramate as adjunctive therapy in refractory partial epilepsy; pooled analysis of data from five double-blind, placebo-controlled trials. Epilepsia, 38, 531-533.
[16] Loescher W., Schmidt D. (2006) Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. Epilepsia, 47, 1253-1284.
[17] Glauser T.A. (1997) Topiramate. Semin Pediatr Neurol, 4, 34-42.
[18] Biton V., Edwards K.R., Montouris G.D. (2001) Topiramate titration and tolerability. Ann Pharmacother, 35, 73-179.
[19] Bialer M., Doose D.R., Murthy B., Curtin C., Wang S.S., Twyman R.E., Schwabe S. (2004) Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 43(12), 763-780.doi:10.2165/00003088-200443120-00001.
[20] Caldwell, G.W., Wu, W.N., Masucci, J.A. (2005) European Journal of Drug Metabolism and Pharmacokinetics, 30, 151-164. doi:10.1007/BF03190614
[21] Faught E., Wilder B.J., Ramasy R.E. (1996) Topiramate-controlled dose-ranging trial in refractory partial epilepsy using 20-, 400-, and 600-mg daily dosages. Topiramate YD Study Group, Neurology, 46, 1684-1690.
[22] Shorvon S. (1996) Safety of topiramate: Adverse events and relationships to dosing. Epilepsia, 37(Suppl 2), S18-S22. doi: 10.1111/j.1528-1157. 1996.tb06029.x
[23] Merino-Salas S., Arrabal-Polo M.A., Cano-Garcia Mdel C., Arrabal-Martin M. (2014) Calcium nephrolithiasis induced by topiramate. Arh Esp Urol, Apr;67(3), 284-287.
[24] Dumitraşcu V., Matusz Anca Alexandra, Cinca Rodica, Grecu Daniela Ştefania (2004) Drug-induced calculi. Identification, structure and composition. Archives of the Balkan Medical Union, 40, 31-37.
[25] Wilner A., Raymond K., Polland R. (1999) Topiramate and metabolic acidosis, Epilepsia, 40, 792-795.
[26] Kuo R.I., Moran D.E., Kim D.H. (2002) Topiramate-induced nephrolithiasis. J Endourol, 16, 229-231.

[27] Matusz Anca Alexandra (1995) The value of some complex investigations in the study of kidney stones and microlithiasis in children. PhD Thesis, elaborated at "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania.

[28] Thambi L., Kapcala L.P., Chambers W. (2002) Topiramate-associated secondary angle-closure glaucoma: a case series. Arch Ophtalmol, 120(8), 1108. doi:10.1001/archopht.120.8.1108

[29] Stella F., Caetano D., Cendes F., Guerreiro C.A.M. (2002) Acute psychotic disorders induced by topiramate. Report of two cases. Arquivos de Neuro-Psiquiatria, 60(2), 1678-1680. http://dx.doi.org/10.1590/S0004-282X2002000200019

*Corresponding author.
E-mail address: anca.matusz@ gmail.com