REVIEW

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Clinical and pathological features of splenic metastasis from cervical squamous cell carcinoma

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Abstract

Isolated splenic metastases from squamous cell carcinoma (SCC) of the cervix are rare, with few cases reported in the literature. We review here the main clinical and pathological findings in these patients, with emphasis on histopathological features. Because they are so rare, complex follow-up protocols for patients diagnosed with cervical SCC should exist because, if detected and treated, solitary splenic metastases seem to have a better prognosis than splenic metastases as part of a disseminated disease.

Keywords: squamous cell carcinoma, uterine cervix, gynecological tumors, splenic metastasis.

Introduction

Squamous cell carcinoma (SCC) of the cervix is the second most common cancer in females [1]. In advanced stages, it presents with local extension into the para-cervical tissues and local-regional dissemination into lymph nodes. The lymphatic and/or hematogenous metastasis to other sites is rare and occurs most commonly in the supraclavicular and para-aortic lymph nodes, lungs, liver, bones. Metastases can occur also in atypical sites like skin, gallbladder or pericardium but in most of these cases only in the context of disseminated disease [1–4]. Among these atypical sites, splenic involvement is clinically detected exceptionally and, therefore, only occasionally reported [5–7].

The advancement of diagnosis and treatment procedures regarding the management of cervical carcinoma has led to better control of the disease and extended survival of patients, thus increasing the frequency of distant metastasis detection [8, 9]. However, splenic metastasis of cervical carcinoma remains a very rare event, divided equally between splenic involvement as part of a disseminated disease and solitary metastases [5].

Epidemiology

The spleen is an uncommon site for metastases [4]. From a series of 7165 cases of carcinomas assessed by Berge, more than four decades, 312 (7.1%) presented metastases to the spleen, of which only eight cases were carcinomas of the uterine cervix. The primary tumors that most frequently develop splenic metastases are breast carcinoma, lung carcinoma, and melanoma [10]. A more recent study of Compérat *et al.* confirms these findings and further identifies colorectal and ovarian carcinomas as the most common primary source of solitary splenic metastases [11]. Moreover, splenic extension of a carcinoma originating in the exocervical mucosa is exceedingly rare. Thus, from the first case published by Brufman *et al.*, in 1977 [12], we succeeded to identify only fourteen cases presented either as abstract or full text in international databases, including our case published in 2017 [13].

From all these cases, we found no data available in the *PubMed Abstract* only for the case reported by Zamurovic *et al.*, in 2011 [14]. In Table 1 are listed some of the main clinical features of these cases. Apart from the selected cases, other three cases had in addition to the splenic involvement a second and third metastatic site, *i.e.*, the liver [2], the breast [15], and the pancreas together with the left supraclavicular lymph node [16].

Pathogenesis

It was thought that majority of the secondary carcinomas in the spleen are the result of hematogenous dissemination [17]. However, it is assumed that the scarcity of spleen metastases of cervical carcinoma is due to the spread *via* local invasion and lymphatics, rather than hematogenous spread [8]. Further, Berge [10] and other authors [2, 18–20] identified two main groups of factors that could explain this rarity:

(a) Mechanical factors that prevent the penetration into the splenic artery of blood-circulating tumor emboli, including:

- The presence of a splenic capsule;
- The sharp angle of splenic artery branching from the celiac artery;
- The tortuosity of the splenic vessels;
- The rhythmic contraction of splenic capsule;

▪ The constant flow of blood through the spleen;
▪ The lack of afferent lymphatic vessels.
(b) Biological factors:
▪ The inherent immunity, expressed by the ability of producing or not of anti-tumor antibodies;
▪ The concentrated presence of phagocytes in the spleen;
▪ The inhibitory effect of the splenic microenvironment pro-apoptotic signals that results in the failure of metastatic cells growth and survival.

Clinical features

Patient's complains

The low incidence of spleen metastases may have been underestimated because in 80% of cases they are asymptomatic [2]. In symptomatic cases, the clinical sign that most frequently triggered further investigations was pain in the left abdomen and especially in the left hypochondrium, sometimes accompanied by moderate, intermittent fever or weight loss. This was associated in some cases with splenomegaly, or, in only one case, with spontaneous rupture of the spleen [21–23].

Patient's age

For age analysis, three groups were defined: I – <40 years, II – 40–49 years, and III – >50 years. Thus, we observed that more than three quarters of the patients were gathered in the groups II and III, meaning older than 40 years and only three patients were young, having around 30 years of age (Table 1).

Primary tumor clinical stage

Incipient stages of cervical epithelial malignant proliferations are more frequently associated with a risk of local recurrence whereas the likelihood of distant metastasis increases with FIGO (*International Federation of Gynecology and Obstetrics*) stage [24], being the highest in disseminated disease [1–4, 25].

However, in the group of patients with solitary splenic metastases, most of the cases (10 out of 13) were in the FIGO stage II, especially in IIB subgroup, and had no signs and histopathological proofs of spread to regional lymph nodes or to tissues within the pelvis (Table 1). This seems to diverge from the typical pattern of spreading described above, in which lymph node involvement precedes visceral metastases, and could suggest different molecular mechanisms are involved.

Disease-free interval (DFI)

For the DFI analysis, three groups were defined, depending its length in months: I – <12 months (less than one year), II – 13–36 months (between two and three years), and III – >37–60 months (between four and five years). Solitary splenic metastases were usually detected after an interval of more than three years, going to five years from the clinical detection of the primary disease, located in the cervix, ranging between 10 and 60 months (median 39 months), in accordance with other literature estimations [5, 7], but sometimes they can occur quite rapidly, with no apparent relation to disease stage or age at diagnostic time.

Table 1 – ***Clinical features of reviewed cases***

No.	Ref No.	Complain(s)	Age [years]	FIGO stage	DFI [months]
1.	12	NM	43	IB	60
2.	22	Pain (LA)	28	IIB	57
3.	9	Splenomegaly	47	IIB	48
4.	6	NM	45	IIA	36
5.	26	NM	45	IIA	60
6.	27	No	52	IIB	14
7.	28	Pain (LH), fever, splenomegaly	50	IIB	42
8.	29	No	54	IIB	10
9.	25	Pain (LH)	30	IVA	30
10.	14	No available data in the accessed *PubMed Abstract*			
11.	8	No	49	IIB	10
12.	21	Fever, anorexia	46	IIA	17
13.	30	NM	46	IA	NM
14.	13	No	31	IIB	18

DFI: Disease-free interval; FIGO: International Federation of Gynecology and Obstetrics; LA: Left abdomen; LH: Left hypochondrium; NM: Not mentioned.

The attempt of identifying any statistical correlation between patient's age, primary tumor stage and the time interval till the detection of solitary splenic involvement failed, the *p*-value of χ^2 (chi-square) correlation test being greater than the significance level alpha of 0.05 (Figure 1, a–c).

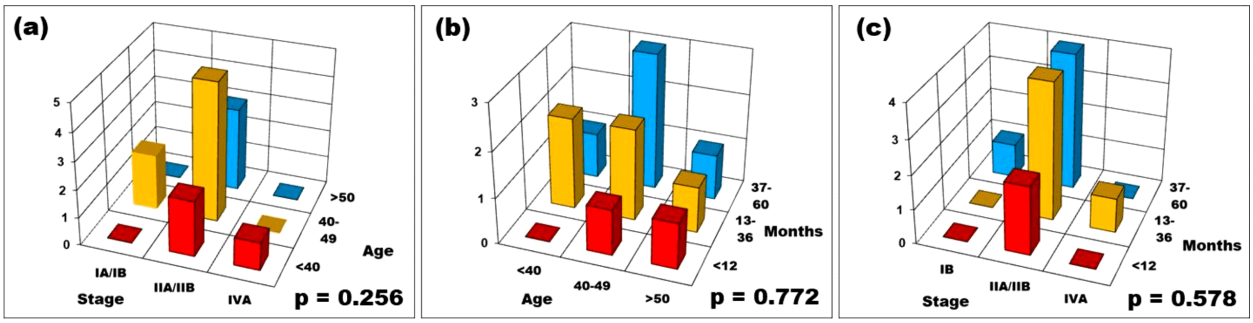

Figure 1 – ***Statistical correlations between clinical parameters – χ^2 test . (a) Patient's age – primary tumor stage; (b) Patient's age – disease-free interval (DFI); (c) Primary tumor stage – DFI.***

Detection of the splenic tumor

Excepting the case reported by Zamurovic *et al.* [14], the presence of the splenic metastasis was suspected and/or confirmed either clinically or biologically but especially by imaging techniques (Table 2).

The splenic metastases had no clinical expression in

almost one-third of the cases. In another third of the cases, the specifically located pain, alone or associated with splenomegaly and/or fever oriented the diagnosis. In only one case, the clinical examination, in conjunction with patient's history, was enough to orient the diagnosis towards splenic metastasis [9]. Unfortunately, in another one third of the cases there was no mention in the report about the clinical examination (Table 2).

Table 2 – ***Methods of splenic tumor detection***

No.	Ref No.	Clinical	TM-ST	IM
1.	14	No available data in the accessed *PubMed Abstract*		
2.	12	NM	NM	NM
3.	9	Yes (splenomegaly)	NT	No
4.	22	Yes (pain – LA)	NT	CAT
5.	28	Yes (pain – LH, fever, splenomegaly)	NT	US
6.	21	Yes (fever, anorexia)	NT	CAT, PET
7.	25	Yes (pain – LH)	SCCA ↑	CAT, PET
8.	13	No	NT	CAT, MRI
9.	8	No	SCCA ↑	CAT
10.	27	No	SCCA ↑	CAT
11.	29	No	SCCA ↑	CAT, PET
12.	30	NM	NM	CAT
13.	6	NM	NT	CAT + FNAB
14.	26	NM	SCCA ↑	CAT, MRI, PET

CAT: Computed tomography scan; FNAB: Fine-needle aspiration biopsy; IM: Imagistic technique; LA: Left abdomen; LH: Left hypochondrium; MRI: Magnetic resonance imaging; NM: Not mentioned; NT: Not tested; PET: Positron-emission tomography; SCCA ↑: Elevated level of squamous cell carcinoma antigen in the serum; TM-ST: Tumor marker(s) serum test; US: Ultrasound examination.

It is true that tumor markers and especially squamous cell carcinoma antigen (SCCA) were not tested in more than 40% of the cases and in other 20% there was no mention about its use or not.

However, when it was used, the serum test showed characteristic elevated levels. In one case [25], rising SCCA preceded clinical signs by six months. It is interesting that there was no clinical expression of the splenic involvement in three of the five cases where SCCA was tested [8, 26, 27, 29], the test being used for the surveillance of the treatment applied for the primary tumor.

More than two decades ago, Crombach *et al.* showed that SCCA serum levels are influenced by the infiltrative growth, the mass, and the degree of histological differentiation of the tumor [31]. Therefore, SCCA can be used for the monitoring of SCC of the cervix evolution, response to treatment, and recurrences, its serum levels being elevated before the occurrence of symptoms [26, 29, 32]. Furthermore, in reviewed cases, increase in SCCA serum levels prompted further explorations in order to confirm the diagnosis in all cases it was used [8, 25–27, 29]. Ikeda *et al.* also underlined the utility of CEA (carcinoembryonic antigen) in monitoring patients with surgically treated cervical SCC [33].

The analysis of the detection methods of splenic secondary tumors revealed that imagistic techniques seem to be the golden standard for splenic involvement investigation. Excepting the above-mentioned case [9], where the clinical examination was considered enough for the diagnosis and other two cases where there were no available data [12, 14], in all the other reviewed cases, the imaging examination either confirmed [8, 21, 22, 25–29] or even detected [6, 13, 30] the isolated splenic involvement following a previous cervical SCC.

The procedure of choice was computed tomography scan (CAT), which was completed in four cases [21, 25, 26, 29] with positron-emission tomography (PET) and in two cases with magnetic resonance imaging (MRI) (Figure 2) [13, 26].

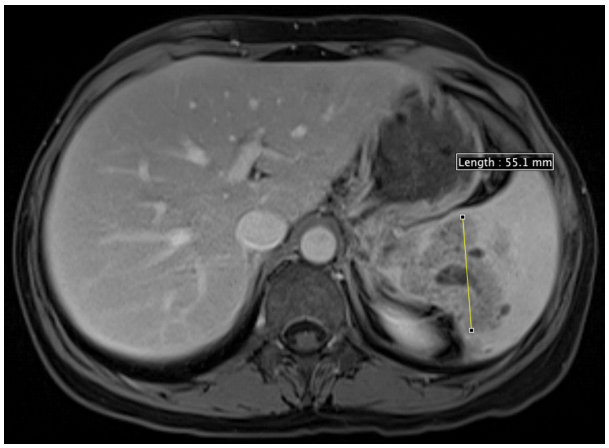

Figure 2 – ***Case Ref. No. [13]: MRI showing isolated tumoral mass of 5/5 cm, located in the splenic hylum.***

There was also one case where the imaging technique of choice was the ultrasound examination (US) [27]. It has to be noted that, in one case [6], the diagnosis algorithm was completed by an invasive but very precise technique (accurate in about 90% of cases), *i.e.*, fine-needle aspiration biopsy (FNAB). The technique is rarely used in the diagnosis of splenic metastases because of the possible risk of hemorrhagic complication (spleen being a highly vascular organ). However, the procedure is less aggressive than the surgical approach and allows avoidance of unnecessary splenectomy in case of benign splenic lesions, such as granulomatous disease [11, 34].

Pathology

Splenic metastases can present as four main morphological patterns. Three of them can be detected macroscopically: the nodular pattern with its two variants, macronodular or micronodular and the diffuse pattern. The fourth pattern is the microscopic one [10].

In the reviewed cases, splenic metastases had mostly a gross morphology of nodular masses, ranging between 2 cm and 19 cm in the largest diameter (Figure 3).

However, in two cases [9, 28], the nodules with large enough dimensions (7 cm and 19 cm, respectively) proved to be cystic formations.

Whatever the pattern of splenic infiltration, the splenic metastasis and primary tumor are generally similar in terms of cytological and architectural aspect [11]. This statement is not entirely confirmed in the case of solitary metastases in the spleen of cervical SCCs.

Excepting the cases of Brufman *et al.* [12] and Zamurovic *et al.* [14], where no data were available, it

is interesting to point out that 40% of the remaining 12 cases had not a detailed description of the morphology and the degree of differentiation of neither the primary tumor of the cervix nor the secondary tumor in the spleen. From the remaining seven cases, the histopathological diagnosis was the same in the primary and metastatic tumors in only three of them [8, 27, 29]. In the other four cases [13, 21, 25, 28], the histopathological pattern of the secondary tumors in the spleen was worse than that of the primary cervical tumor (Table 3).

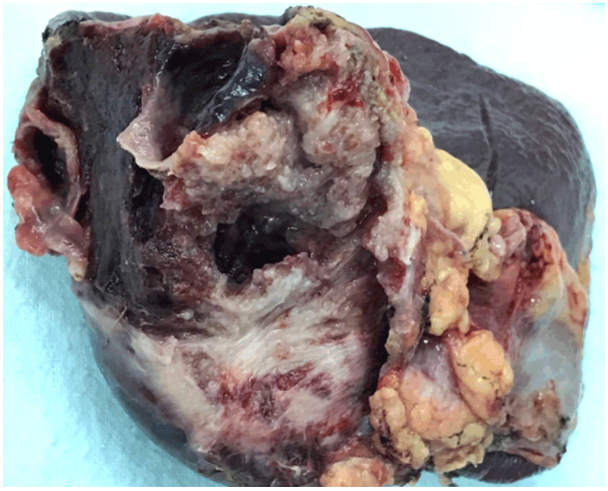

Figure 3 – ***Case Ref. No. [13]: Gross appearance of the spleen showing non-homogenously colored structure in the splenic hylum.***

Table 3 – ***Histopathological assessment of primary and secondary tumors***

No.	Ref No.	Cervix	Spleen	Correspondence
1.	14	NM	NM	No data available
2.	12	NM	NM	
3.	22	SCC NOS	SCC NOS	No specification concerning morphology/ differentiation
4.	9	SCC NOS	SCC NOS	
5.	6	SCC NOS	SCC NOS	
6.	26	SCC NOS	SCC NOS	
7.	30	SCC NOS	SCC NOS	
8.	29	SCC K	SCC K	The same
9.	27	SCC NK	SCC NK	
10.	8	C Undiff	C Undiff	
11.	28	SCC NOS	SCC K	Worse
12.	13	SCC NOS	SCC MD	
13.	25	SCC MD	SCC PD	
14.	21	SCC MD	SCC PD	

C: Carcinoma; K: Keratinized; MD: Moderately differentiated; NK: Not Keratinized; NM: Not mentioned; NOS: Not otherwise specified; PD: Poorly differentiated; SCC: Squamous cell carcinoma; Undiff: Undifferentiated.

The morphological microscopic identification of SCCs, especially of those with a high and even moderate degree of differentiation should not be a problem for an experienced pathologist. The presence of squamous epithelial cells, usually large, with abundant eosinophilic cytoplasm, and a large, often vesicular, nucleus and a variable degree of keratinization arranged in nests invading the normal neighboring tissue constitutes the hallmark of this type of epithelial malignant proliferations (Figure 4, a and b). Sometimes a stromal desmoplastic reaction surrounds the nests of tumor cells (Figure 4d).

Sometimes, however, when the degree of differentiation is decreasing, as in primary and secondary tumors reported by Taga *et al.* [8] and Komatsu *et al.* [27] or only in secondary tumors reported by Dixit *et al.* [21] and Di Donato *et al.* [25], immunohistochemical (IHC) techniques could be of valuable help. The most common choice is the use of the antibody cocktail containing cytokeratin (CK) 5/6, p16, and even p14 (Figure 4, e–g), markers overexpressed in cervical squamous carcinomas, p16 signaling also the association with high-risk human papillomavirus (hrHPV) [21, 35–37]. This antigen cocktail is useful to confirm the squamous origin of splenic and even cervical proliferations with undifferentiated morphological features when this origin is primarily suggested by the serum levels of SCCA.

Another IHC marker whose use could be of benefit in the investigation of solitary splenic metastases of SCC of the cervix is Ki67 (Figure 4h). Its assessed index could signal the increase of tumor proliferation rate [38], could predict the metastatic potential if used during the early course of radiotherapy [39] or could have a prognostic value for overall survival [40].

Finally, another IHC marker that could be used is p53 (Figure 4i). However, even the loss of p53 tumor suppressor gene function, considered as the commonest genetic alteration involved in human malignancies, is included among the co-factors influencing the multistep process of the uterine cervix carcinoma pathogenesis, there is no evidence to suggest that its overexpression may be useful as a prognostic indicator [41, 42].

Treatment

Treatment of the primary disease was administered to reviewed patients according to the relevant protocols that generally included initial radiotherapy (including external beam radiation therapy and brachytherapy), surgery, and, for some of the patients, subsequent chemotherapy. Thus, surgery was the only procedure in three cases [6, 12, 27], associated with radiotherapy in other three cases [21, 26, 30], and with chemotherapy in one case [25]. Radiotherapy was the only procedure in three cases [9, 22, 28] and associated with chemotherapy in other two cases [8, 29].

There was only one case where the algorithm has been fully covered [13] (Table 4).

So, the algorithm did not include always all the steps, being adapted to the patient's status at the admission for the primary tumor. When the spleen metastasis is found, there are usually multiple organ metastases and surgery is not indicated [8].

However, in the case of solitary splenic metastases the treatment of choice is splenectomy, the main reasons being:

- Confirmation of the tumor histopathology;
- Avoidance of complications like splenic rupture, splenic vein thrombosis and painful splenomegaly;
- Prevention of further metastatic disease having as source the secondary splenic tumor [19].

Moreover, since it is considered distant metastasis, Dixit *et al.* stated that chemotherapy should follow surgery in all cases of splenic metastasis [21].

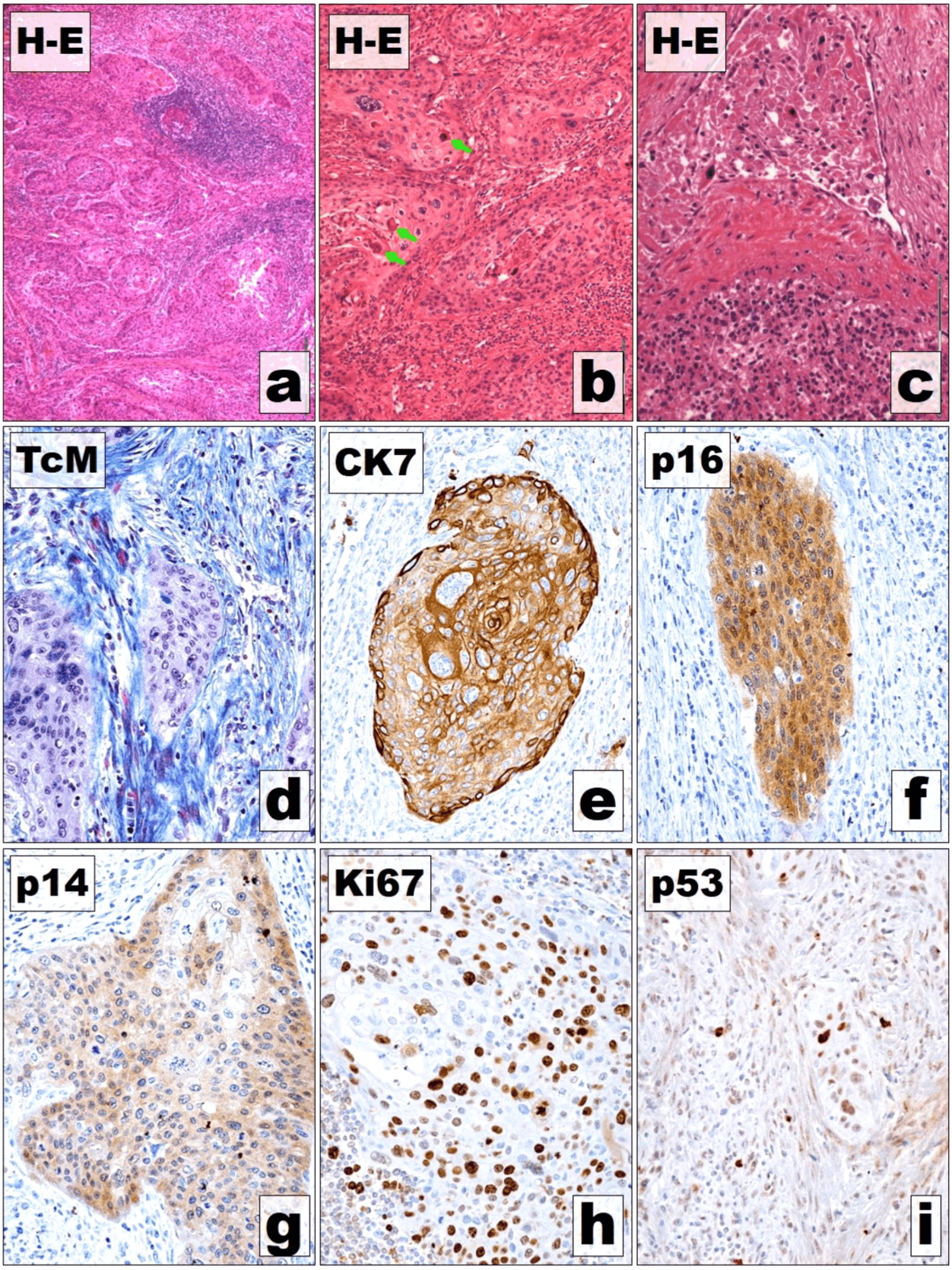

Figure 4 – ***Histological features of squamous cell carcinoma (SCC) in the spleen: (a) Nests of SCC invading the spleen parenchyma – residual areas of normal white pulp are seen [Hematoxylin–Eosin (HE) staining, ×50]; (b) Islands of typical SCC, including individual densely keratinized cells (arrows) (HE staining, ×50); (c) Tumor vascular embolus (HE staining, ×200); (d) Desmoplastic reaction around tumor islands (Masson's trichrome staining, ×400); (e–g) Immunohistochemical (IHC) cocktail – cytokeratin (CK) 7, p16 and p14 – for SCC identification (×200); (h) Ki67 staining (×200); (i) p53 staining (×200).***

Table 4 – ***Therapeutic strategy and follow-up of cases with isolated spleen metastasis of SCC of the cervix***

No.	Ref No.	Age [years]	FIGO stage	Primary treatment	Secondary treatment	Follow-up*	Survival*
1.	12	43	IB	Surgery	ChT	11	Yes/71
2.	22	28	IIB	EBRT	Surgery, ChT	19	Yes/76
3.	9	47	IIB	EBRT	ChT	15	Yes/63
4.	6	45	IIA	Surgery	ChT	12	No/48
5.	26	45	IIA	Surgery, RT	Surgery, ChT	5	Yes/65
6.	27	52	IIB	Surgery	Surgery	12	Yes/26
7.	28	50	IIB	RT	Surgery	48	Yes/90
8.	29	54	IIB	EBRT, ChT	Surgery, RT, ChT	25	Yes/35
9.	25	30	IVA	Surgery, ChT	Surgery, ChT	12	Yes/46
10.	14	No available data in the accessed *PubMed Abstract*					
11.	8	49	IIB	ChT, RT	Surgery, ChT	20	Yes/30
12.	21	46	IIA	Surgery, RT	Surgery, ChT	2	Yes/19
13.	30	46	IA	Surgery, EBRT	Surgery	NM	Yes/NM
14.	13	31	IIB	Surgery, RT, ChT	Surgery, ChT	12	Yes/30

ChT: Chemotherapy; EBRT: External beam radiation therapy; FIGO: International Federation of Gynecology and Obstetrics; NM: Not mentioned; RT: Radiotherapy; *: In months, at the moment of publication.

In reviewed cases, splenectomy was indeed the first step in the secondary treatment algorithm in more than three quarters of cases with available data. Chemotherapy followed the surgery in 70% of these cases. However, there were some cases where, depending on case particularities, the "two steps" therapeutic algorithm was incomplete. Thus, in three cases [27, 28, 30], splenectomy was the only therapeutic procedure and, in other three cases [6, 9, 12], chemotherapy was the only possible therapeutic procedure (Table 4).

In only one case, the radiotherapy completed the therapeutic protocol because five months after splenectomy, CT and PET scan showed a 2.5 cm recurrent mass in the perirectal spaces and cul de sac [29].

Follow-up, outcome

While splenic metastases as part of a disseminated disease are associated with poor prognosis, solitary splenic metastases represent a more moderate disease [5]. Compérat *et al.* remark the long-term remission achieved by splenectomy alone in patients with late occurrence of splenic metastasis [11]. In the reviewed cases, the follow-up after secondary therapy varied between two and 48 months but the assessment covered only the time period till the publication of the case. The overall survival from the moment of primary tumor discovery varied between one year and a half [21], and seven years and a half [28].

At the time of case publication, there was only one patient who died [6], all the other being alive (Table 4).

The attempt of identifying any statistical correlation between patient's age, primary tumor stage and the follow-up time after secondary treatment also failed, the *p*-value of χ^2 correlation tests being greater than the significance level alpha of 0.05 (Figure 5, a and b).

According to Badib *et al.*, the leading causes of death could be renal failure, sepsis and respiratory failure [43]. However, due to the uncommon nature of the lesion and the absence of relevant studies, prognosis is difficult to determine.

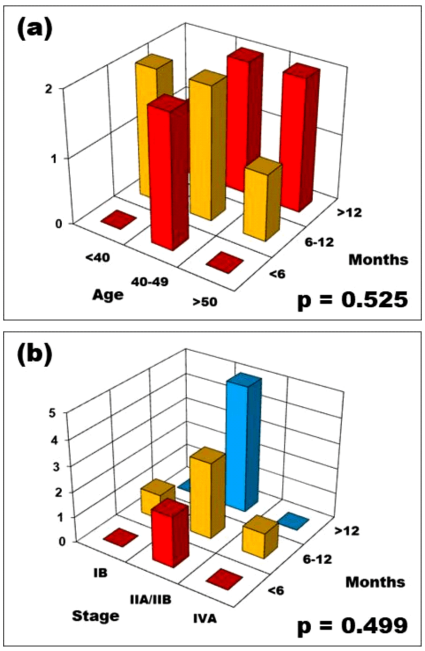

Figure 5 – ***Statistical correlations between clinical parameters – χ^2 test: (a) Patient's age – follow-up after splenectomy; (b) Primary tumor stage – follow-up after splenectomy.***

Conclusions

Solitary splenic metastases of SCC of the cervix are a peculiar event in the evolution of primary tumors whose appearance and prognosis seem to have no relation with patient's age and FIGO stage of the primary tumor. However, just because they are so rare, follow-up protocols for patients diagnosed with cervical SCC should be complex, including periodical anamnesis, clinical examination, vaginal cytology, serum tumor markers, and imaging investigations because, if detected and treated, solitary splenic metastases seem to have a better prognosis than splenic metastases as part of a disseminated disease.

Conflict of interests

The authors declare that they have no conflict of interests.

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