Recurrent cervical smear abnormalities following treatment

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The cervical screening programme has had a dramatic impact on the incidence of invasive cervical cancer and preinvasive disease can be effectively treated in the majority of cases. However, recurrent abnormalities after treatment pose management dilemmas which are considered in this overview of the topic.

Exfoliative cytology involves the examination of a smear of cells taken from the area of the cervix around the external cervical os and cervical canal, known as the transformation zone, in order that both types of cervical cell, squamous and columnar, are sampled. The objective is to detect dyskaryotic cells, which are neoplastic with nuclear abnormalities, such that appropriate investigation and management can be instigated. Significant and persistent abnormalities require assessment by colposcopy, resulting in a definitive tissue diagnosis and treatment if this is indicated.

The cervical screening programme has had a significant impact on the incidence of invasive cervical cancer because of the widespread detection of pre-invasive disease and its effective treatment. The incidence of invasive carcinoma of the cervix in England and Wales fell from 16.1 new cases per 10^5 women in 1986 to 11.2 per 10^5 in 1993, with the number of deaths in England falling by over 40% between 1979 and 1995 (Duncan, 1997).

The treatment modalities for all grades of cervical intraepithelial neoplasia (CIN) may be:

- Destructive, including cryosurgery, cold coagulation, laser vaporization, electrocautery and electrodiathermy
- Excisional, including conization using laser, loop diathermy (large loop excision of the transformation zone; LLETZ) or a knife, and hysterectomy.

The most widely used methods in current practice are excisional, particularly LLETZ, and excisional methods should always be employed in cases of cervical glandular intraepithelial neoplasia (CGIN).

While the treatments are generally effective, there is an increased risk of further abnormalities occurring in these women, both pre-invasive and invasive disease (Burghardt and Holzer, 1980). In addition, the occurrence of post-treatment dyskaryosis may cause considerable management dilemmas. Colposcopic assessment is less reliable after treatment, and concerns regarding the risk of invasive malignancy are heightened in the presence of recurrent smear abnormalities. In addition, compromises may be required in relation to future fertility. In reviewing this topic, the incidence will be considered first before dealing with the management.

INCIDENCE OF POST-TREATMENT DYSKARYOSIS

The majority of series reporting initial 'cure' rates with destructive treatments quote figures in excess of 85% (Coppleson et al, 1992). In a large series of 2130 cases utilizing laser vaporization, there were 119 failures (5.6%), of which 71% were detected in the first year following treatment and 24% during the second year (Paraskevaidis et al, 1991). There have also been reports of invasive cancers developing after ablative treatment for CIN (Pearson et al, 1989; Shumsky et al, 1994), suggesting that established invasive disease may have gone undetected before such therapy. One would expect invasive tumours to be picked up by appropriately performed excisional treatment (Prendiville et al, 1989), and this is one of the main reasons for the move back towards these methods in recent years.

The vast majority of excisional treatments are now performed using LLETZ. In a study analysing the first 1000 women treated with LLETZ in Aberdeen from 1989 to 1991, the cumulative rate of recurrence at 4 years in 317 women followed up for that length of time was 10.1% (Flannelly et al, 1997). There was one

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case of microinvasive disease. In a series of 123 patients treated by laser conization, four patients developed recurrent disease during a median follow-up of 30 months (Vergote et al, 1992). With regard to knife cone biopsy, 201 patients treated for CIN during a 5-year study had a reported success rate of 92% (Tabor and Berget, 1990). van Nagell et al (1985) found no cases of recurrent disease in a group of 144 women treated by hysterectomy for CIN III on colposcopically directed biopsies with follow-up from 1–10 years. However, in 993 women treated with hysterectomy for CIN, of whom 793 completed 10 years of cytology and colposcopy follow-up, 41 developed vaginal intra-epithelial neoplasia (VAIN) (Kalogirou et al, 1997).

The incidence of post-treatment dyskaryosis may be affected by a number of factors, including deviation from accepted standard colposcopy protocol (Shumsky et al, 1994). Length of follow-up will obviously influence the number of recurrent cases, and Soutter et al (1997) reported that while conservative outpatient therapy in women with CIN reduced the risk of invasive cancer of the cervix by 95% during the first 8 years after treatment, even with careful, long-term follow-up, the risk of invasive cancer was about five times greater than among the general population. They recommended careful follow-up for at least 10 years after conservative treatment for CIN.

The type of sampling device for taking smears has been implicated in the detection of post-treatment dyskaryosis, with the Ayre's spatula being superior to the Aylesbury, the Rocket and the Multispatula device. The Cytobrush did not substantially improve the detection rate of dyskaryosis (Hughes et al, 1992).

In a series of 642 patients treated for CIN with either laser ablation or LLETZ, the presence of human papillomavirus (HPV) infection before initial treatment resulted in a higher failure rate (Raju et al, 1995). While less common, infection with human immunodeficiency virus (HIV) is associated with a high recurrence rate (Wright et al, 1994), and such infection may be associated with recurrent CIN despite multiple treatments (Fruchter et al, 1996).

After excisional treatment using LLETZ, the incidence of CIN is increased in cases where the abnormality has been incompletely excised (Shafi et al, 1993; Flannelly et al, 1997; Gardeil et al, 1997). In addition, increased lesion size has been implicated in the risk of abnormal cervical cytology following LLETZ (Shafi et al, 1993).

Finally, the type of cellular abnormality may be important in the prediction of post-treatment dyskaryosis, as Wolf et al (1996) found that women with adenocarcinoma in-situ often have residual disease in the uterus, regardless of whether the margins on cone biopsy were positive or negative.

MANAGEMENT OF POST-TREATMENT DYSKARYOSIS

As in patients newly presenting with dyskaryosis, one should bear in mind the limitations of cervical cytology and the possibility of a false-positive report, which may be caused by immature physiological metaplastic epithelium, acute inflammation produced by various infections, atrophic conditions of the epithelium associated with hypoestrogenism and HPV infection without atypia (Coppleson et al, 1992). A further problem, particularly seen in women who have been treated for CIN or CGIN, is that of tubo-endometrioid metaplasia which may be confused with dyskaryosis and result in unnecessary further treatment (Hirschowitz et al, 1994).

Unless the source of post-treatment dyskaryosis is a clinically obvious invasive cancer of the cervix, a very thorough colposcopic assessment should be made of the cervix and vagina. Following treatment for pre-invasive disease, the topography of the transformation zone has been altered (Soutter, 1997), with the result that isolated iatrogenic skip lesions surrounded by columnar epithelium or covered by new squamous epithelium may occur. Consequently, the colposcopist cannot rely on visualization of the squamocolumnar junction excluding any abnormality further up the cervical canal, and treatment if indicated should be by excision and not destruction.

Following the colposcopic assessment, possibly including further cytology specimens, one has to make a decision on whether or not treatment is required and, if so, on the most appropriate technique. A number of important factors will require consideration including the patient's age and desire for future pregnancy as well as her wishes regarding surgical intervention, along with the type of dyskaryosis and severity of disease, its location and the original treatment employed. A clinically obvious invasive carcinoma should be staged and managed according to standard protocols. In discussing the management of other cases, the following situations need consideration:

Squamous dyskaryosis with colposcopic abnormality confined to the cervix

Because of the altered topography of the cervix after treatment, colposcopic assessment can never be entirely satisfactory and its main role is in predicting the severity of the abnormality and

its distal extent. Because of the risk of false-positive dyskaryosis in these patients as well as possible difficulties in colposcopic differentiation of CIN from immature squamous metaplasia, one would normally confirm the diagnosis with colposcopically directed biopsies before embarking on definitive treatment.

Clearly, one should only treat patients with CIN, and the decision on whether or not to treat CIN I will be influenced by the woman's views after appropriate counselling. Unless she were very keen to be treated, it would be reasonable to keep her under close surveillance in the hope that the abnormality would regress spontaneously.

CIN II or III and lesions where colposcopic assessment is suggestive of invasion should be treated. Shafi et al (1993) recommended that excision biopsy be performed if follow-up cytology showed moderate or severe dyskaryosis, especially if still present 12 months after treatment. The type of excisional treatment will depend on the individual factors referred to above.

Squamous dyskaryosis with colposcopic abnormality involving the cervix and vagina

Treatment may be somewhat complicated by extension onto the vagina, particularly if the abnormality is present some distance below the cervix. Again, it would be reasonable to adopt an expectant approach to grade I disease.

Lesions deemed to require treatment should certainly be excised at the upper end, but it may be appropriate to use destructive techniques such as laser ablation on the vagina if there is no colposcopic suspicion of invasion and multiple punch biopsies of the vagina are reassuring. In other situations, vaginal excision may be necessary and because of the difficulty of repairing the cervix after conization with removal of vaginal skin, one may be inclined to recommend hysterectomy with removal of a vaginal cuff taken either vaginally or abdominally. Occasionally, there may be very extensive vaginal disease and while surgical excision may be possible, hysterectomy followed by vaginal radiotherapy may produce less morbidity, particularly in older women.

Glandular dyskaryosis

There are considerably less data available on the management of CGIN than CIN. In the primary management of this abnormality, it has been suggested that diathermy loop excision is adequate (Houghton et al, 1997). However, there have been other reports of frequent residual uterine disease after treatment (Wolf et al, 1996).

Long-term follow-up, including endocervical cytological sampling, is essential. Colposcopic assessment is important in post-treatment glandular dyskaryosis, although it has significant limitations, not least because of the location of most glandular lesions above the external cervical os.

Treatment of recurrent glandular disease must be excisional and, unless the patient's circumstances preclude hysterectomy, should probably involve this technique. After a second conization procedure, the risk of a further glandular abnormality occurring must be considerable and its detection may be significantly hampered by anatomical distortion of the cervical canal.

Vaginal dyskaryosis after previous hysterectomy

Vaginal dyskaryosis poses significant management problems, and its assessment requires considerable colposcopic experience. Following hysterectomy, vaginal epithelium may become buried above the vault suture line and consequently disease in this location may not be visible. There may be extensive disease, the treatment of which can cause major morbidity.

Laser vaporization of VAIN was widely practiced during the 1980s and there were encouraging reports of this (Sherman, 1990). However, other series noted disappointing results (Woodman et al, 1984), thought to be the result of inaccessibility of abnormal areas of epithelium. VAIN at the vaginal vault should therefore be treated by excision, although the laser may have a role in treating more distal disease.

Excision of vaginal disease may be achieved by an abdominal approach, a combined abdominal and vaginal approach, or by a vaginal approach (Ireland and Monaghan, 1988; Curtis et al, 1992), and gives excellent results.

In other circumstances, particularly older women with a narrow introitus, one may consider vaginal radiotherapy which has been found to be effective in eradicating pre-invasive disease (Woodman et al, 1988). However, cytological follow-up may be compromised in the presence of irradiated tissues and long-term colposcopic surveillance is recommended.

The follow-up of patients who have presented with post-treatment dyskaryosis, whether or not it required further treatment, should be vigilant. A combined colposcopic and cytological approach should certainly be employed initially. Assuming that such assessments are satisfactory at 6 and 18 months, one could allow annual cytology for up to 5 years after presentation. While such patients are at increased risk of developing further abnormalities in the long term, there are currently no data to suggest that annual screening should be continued beyond 5 years.

Following hysterectomy for CIN or CGIN, it is recommended that screening can be discontinued after two normal smears 6 and 12 months after surgery if the disease has been completely removed (Duncan, 1997). Where excision is uncertain, 3-yearly screening should continue.

In cases of VAIN, it would seem prudent to follow patients up colposcopically as well as cytologically for 5 years with 3-yearly cytological screening subsequently, although there are few data to assist one in optimizing follow-up.

CONCLUSION

While the incidence of invasive cervical cancer is falling as a result of an effective screening programme, post-treatment dyskaryosis is a situation in which the management dilemmas far outweigh the size of the problem. Patient anxiety is understandably heightened by such a cytological abnormality and treatment must be tailored to the individual clinical circumstances in an efficient and expeditious manner. HM

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KEY POINTS

- While conservative treatment for cervical intraepithelial neoplasia reduces the risk of developing invasive cancer by 95% during the first 8 years after treatment, the risk of invasive cancer occurring remains five times higher than in the general population.
- The main risk factors for the development of post-treatment dyskaryosis are incomplete excision, increased size of the lesion, and the presence of human papillomavirus infection at the time of initial treatment.
- Post-treatment dyskaryosis may be suggested by false positive cytology reporting, and thorough colposcopic assessment with biopsies should be performed before embarking on treatment.
- Post-treatment dyskaryosis caused by preinvasive lesions requiring treatment should be dealt with by excisional techniques, except in occasional cases with extensive vaginal disease.